North American Society of Head and Neck Pathology

The Small Round Blue Cell Tumors of the Sinonasal Area

Julia A. Bridge

Departments of Pathology and Microbiology, Orthopaedic Surgery, and Pediatrics,
University of Nebraska Medical Center, Omaha, NE

Contact information:

Julia A. Bridge, M.D., FACMG
Department of Pathology and Microbiology
983135 Nebraska Medical Center
Omaha, NE 68198-3135
Phone: 402-559-7212
Fax: 402-559-6018
Email: jbridge@unmc.edu
Introduction

Head and neck malignancies account for 3-5 percent of all cancers in the United States [1]. Those of the nasal cavity and paranasal sinuses comprise only 0.2-0.8 percent of all malignant neoplasms [2] and because of the close anatomic proximity of the paranasal sinuses with the orbits and skull base, most include disease extension into these structures. Sinonasal malignancies most commonly arise in the maxillary sinus (60%), followed by the nasal cavity (20-30%), the ethmoid sinus (10-15%) and the sphenoid and frontal sinuses (~1%) [2]. Although many different histopathological types of cancer occur in the sinonasal cavity, the most common is squamous cell carcinoma of the maxillary sinus [2]. A poorly differentiated, non-keratinizing squamous cell carcinoma may be difficult to distinguish from olfactory neuroblastoma, neuroendocrine carcinoma or other poorly differentiated, small round blue cell tumors of the sinonasal area.

The “small round blue cell tumors” (SRBCTs) constitute a heterogeneous group of malignant neoplasms characterized by a monotonous population of undifferentiated tumor cells with relatively small-sized nuclei and scant cytoplasm. An early and accurate diagnosis is imperative to allow a patient with a paranasal sinus or nasal cavity SRBCT to undergo the appropriate therapy. However, to effect a definitive diagnosis of a SRBCT based solely on the H & E light microscopic findings may be exceedingly difficult because of the frequent absence of distinguishing features. This diagnostic challenge may be further complicated if the pathologist is confronted with a biopsy of small or limited size. Ancillary studies to include immunohistochemical, ultrastructural, cytogenetic and molecular techniques may be used to aid in the differential diagnosis of SRBCTs.
In this review, emphasis was placed on a diagnostic approach to the differential diagnosis of small biopsy samples of SRBCTs of the sinonasal area. The group of sinonasal SRBCTs reviewed are listed in Table 1.

**Epithelial SRBCTs of the Sinonasal Area**

*Poorly Differentiated, Nonkeratinizing Squamous Cell Carcinoma*

Squamous cell carcinoma (SCC) most frequently arises in the maxillary sinus, followed by the nasal cavity [2]. Analogous to other neoplasms originating in paranasal sinuses, the diagnosis is often delayed because the clinical symptoms are similar to those experienced with chronic sinusitis (nasal obstruction or congestion, facial pain and swelling). In comparison, symptoms of nasal cavity SCC lead to earlier clinical recognition and detection of disease.

Histopathologically, SCC may be easily recognizable if it is of the well-differentiated and/or keratinizing form. Conversely, the poorly differentiated, non-keratinizing variant may exhibit histopathologic features that overlap with other SRBCTs. Recognition of an in-situ carcinoma component and/or direct continuity to the overlying surface epithelium in addition to the presence of broad interconnecting or ramifying cords of neoplastic cells are features not typically identified in the other neoplastic entities presented in this review. Furthermore, cytokeratin immunoreactivity may also be useful for distinguishing this neoplasm from olfactory neuroblastoma (ONB) and the lack of immunoreactivity for synaptophysin, chromogranin, and/or CD56 from small cell carcinoma neuroendocrine type (SCCNET). Franchi et al [3] reported different cytokeratin staining patterns in keratinizing SCC, nonkeratizing SCC, and sinonasal undifferentiated carcinoma (SNUC). In contrast to both keratinizing and nonkeratinizing forms of SCC, SNUC was characterized by the exclusive expression of
cytokeratins of simple epithelia, such as CK8, CK7, and CK19, Table 2. Moreover, SCC is almost always immunoreactive for EMA whereas less than 50% of SNUCs are EMA positive [4].

Recently, an undifferentiated carcinoma with focal squamous differentiation that may arise in the sinonasal area among other midline locations has been described in children and adults [5,6]. This neoplasm, uniquely characterized by rearrangements of the NUT gene may show striking morphologic overlap with NUTwt SCC. The NUT (nuclear protein in testis) gene is localized to 15q14. In addition to molecular or cytogenetic identification of NUT or 15q14 rearrangements respectively, nuclear expression of NUT can also be appreciated by immunohistochemistry in this neoplasm. Interestingly, the majority of the midline carcinomas with NUT rearrangements are associated with a t(15;19)(q14;p13) that gives rise to a BRD4-NUT chimeric oncogene. However, midline carcinomas fusing NUT with a gene partner other than BRD4 appear to have more prominent squamous differentiation and these patients live four-fold longer when compared to patients with BDR4-NUT positive tumors [5].

**Sinonasal undifferentiated carcinoma (SNUC)**

SNUC as defined by the World Health Organization is a rare, highly aggressive carcinoma that typically presents with locally extensive disease [2]. It is more common in males and the affected age range is broad (third to ninth decade). Although of uncertain histogenesis, SNUC does feature unique clinicopathologic characteristics permitting its segregation from other types of epithelial and non-epithelial neoplasms with small round cells.

Clinically, SNUC patients characteristically develop symptoms of relatively short duration (weeks to months) and radiographically, demonstrate large sinonasal lesions that are
typically locally invasive with destruction of orbital and/or cranial bones [7].

Histopathologically, the tumor has a propensity to grow along the mucosal surface, extend into superficial mucosal glands, ulcerate, and invade lymphovascular spaces [2,8]. Individual cells exhibit hyperchromatic to vesicular nuclei, poorly defined cell membranes, high nuclear-to-cytoplasmic ratios and often single, prominent nucleoli. Immunohistochemical stains are not particularly helpful in establishing a diagnosis of SNUC. The tumor cells are immunoreactive for pan-cytokeratins and simple keratins [2,3]. SNUC lacks Epstein-Barr virus (EBV) RNA by in situ hybridization.

**Small Cell Carcinoma, Neuroendocrine Type (SCCNET)**

SCCNET is a high-grade neoplasm that most frequently arises in the superior or posterior nasal cavity with frequent extension into the maxillary and/or ethmoid sinuses [2]. Sinonasal SCCNETs are composed of small to intermediate sized cells with oval or round hyperchromatic nuclei and absent or inconspicuous nucleoli. The tumor cells may be arranged in sheets, nests, and trabeculae and often exhibit extensive apoptosis, confluent necrosis, and hemorrhage. Crush artifact and a high mitotic rate are common [2,9].

SCCNETs of the nasal cavity and paranasal sinuses display morphological and immunophenotypic features that are dissimilar to olfactory neuroblastoma and other sinonasal SRBCTs discussed in this review. Distinction is important because of the differences in prognosis and therapeutic approach. Most are positive for cytokeratin and may show the punctate perinuclear positivity typical of small cell carcinomas arising in other locations [9]. CD56 staining is common whereas staining for synaptophysin, chromogranin and NSE is variable [2]. EBV-RNA is negative by in situ hybridization.
Neuroectodermal SRBCTs of the Sinonasal Area

Olfactory Neuroblastoma

Olfactory neuroblastoma (ONB) is uncommon, accounting for only 1-5% of malignant nasal cavity neoplasms [10]. ONB is thought to originate from the olfactory portion of the mucous membrane lining the nasal fossa and is virtually confined to the upper nasal cavity in the region of the cribiform plate [11,12]. Tumors such as SCCNET, melanoma, sinonasal lymphoma, and SNUC can develop in the same anatomical region as ONB and all can present with similar clinical, histological, and radiological features [10]. Even in the hands of an experienced pathologist, arriving at an accurate diagnosis may be challenging. Misdiagnoses are most commonly encountered in poorly sampled cases or with cases exhibiting extensive crush artifact or divergent differentiation [10,13]. When present, features regarded as diagnostic of ONB and useful in distinguishing ONB from the aforementioned SRBCTs include the presence of fibrillary cell processes, Homer Wright rosettes, and S100-positive sustentacular cells [11,13].

Early cytogenetic studies that have subsequently been disproven, suggested that ONB was a peripheral primitive neuroectodermal family member. In contrast to pPNET, ONB is not immunoreactive for CD99. Most recently, array comparative genomic hybridization (aCGH) studies have shown complex gene copy number profiles with gain of 13q, 20q and loss of Xp as most frequent in high stage tumors [14].

Sinonasal Mucosal Malignant Melanoma

The histologic appearance of sinonasal malignant melanomas may be variable, however, it is the amelanotic variant with small cell morphology that may be especially prone to misclassification, resulting in inappropriate clinical management [15]. Malignant melanoma
occurs within a wide age range and arises more commonly in the nasal cavity than in the paranasal sinuses [2,15]. Most are grossly polypoid and approximately half will demonstrate a brown or black pigmented surface [10]. Diffuse staining for S-100, HMB45 and vimentin as well as the light microscopic appearance of detectable melanin pigment (the latter observed in approximately 2/3 of cases) is useful in distinguishing this high grade malignancy [2,10,15].

**Extraskeletal Ewing’s sarcoma/Primitive Neuroectodermal Tumor**

Similar to ONB, Ewing’s sarcoma/peripheral Primitive Neuroectodermal Tumor (ES/pPNET) usually affects a younger patient. The morphologic and immunophenotypic diversity of ES/pPNET may create diagnostic difficulties [16]. For example, some ES/pPNETs exhibit histological, immunohistochemical, and ultrastructural epithelial features [17]. Others may demonstrate staining for neuroendocrine markers. With the exception of the rare sinonasal desmoplastic small round cell tumor [18], synovial sarcoma [10] or lymphoma [19], CD99 immunoreactivity is useful in distinguishing ES/pPNET from most other sinonasal SRBCTs. Identification of the characteristic t(11;22)(q24;q12) or EWSR1-FLI1 fusion transcript or defined variant translocation can be invaluable in confirming this diagnostic entity.

**Mesenchymal SRBCTs of the Sinonasal Area**

**Desmoplastic Small Round Cell Tumor**

Notably a single case of sinonasal desmoplastic small round cell tumor (DSRCT) has been reported [18]. The importance of this remarkably unusual presentation could come into play if the pathologist is presented with a biopsy of limited size as this entity may exhibit overlapping histologic and immunohistologic features with other sinonasal SRBCTs. Recognition of the
multidirectional immunohistochemical differentiation pattern and the tumor-specific genetic findings \([t(11;22)(p13;q12)\) and associated \(EWSR1-WTI\) fusion transcript] are necessary for definitive diagnosis.

**Rhabdomyosarcoma**

Both embryonal and alveolar rhabdomyosarcoma (ERMS and ARMS respectively) frequently occur in the nasal cavity and sinuses [2]. Although these entities usually predominate in children and young adults, a recent study has illustrated ARMS involvement in older adults (median age, 61 years) [20]. In this study, establishing the diagnosis of ARMS was complicated by its rarity in this age group, lack of an alveolar pattern, and initially misleading immunoprofile (CD56, cytokeratin, and synaptophysin immunoreactivity with lack of inclusion of myogenic markers in the first set of immunohistochemical markers assessed). In addition to synaptophysin expression, some ARMSs also show keratin expression that may lead to a potential misdiagnosis of SCCNET, SNUC, or ONB [21]. Distinguishing ERMS and solid pattern ARMS may be exceedingly difficult without the use of genetic approaches for the identification of the 2;13 and 1;13 translocations or respective \(PAX3-FOXO1\) and \(PAX7-FOXO1\) fusion transcripts. Recently \(PAX3\) variant translocations that create a chimeric oncogene with an \(NCOA\) family member in place of \(FOXO1\) have been described in RMS cases, including a skull-based lesion [22].

**Poorly Differentiated Synovial Sarcoma**

The head and neck region is the second most common site of involvement for synovial sarcoma, although cases arising in the sinonasal tract are rare [10,23]. SS has previously been described in the frontal, maxillary, ethmoid, and sphenoid sinuses [23]. SS causes the greatest
diagnostic difficulties with other sinonasal tumors when it is poorly differentiated with small cell morphology. In this setting, cytokeratin, EMA, BCL2, and TLE1 immunoreactivity coupled with cytogenetic, FISH or molecular confirmation of the t(X;18)(p11.2;q11.2) or derived SYT-SSX chimeric transcripts facilitates an absolute diagnosis.

**Hematolymphoid SRBCTs of the Sinonasal Area**

**Extramedullary Plasmacytoma**

Extramedullary plasmacytoma (EMP) chiefly affects adults older than 65 years of age and involves the sinonasal/nasopharyngeal area in 75% of the cases [24]. Poorly differentiated tumors (immature plasma cells) are the most difficult to recognize and may result in diagnostic confusion with other sinonasal SRBCTs. For example, due to occasional EMA or cytokeratin positivity, EMP may be misdiagnosed as a carcinoma. Diagnostic confirmation can be achieved by immunohistochemistry or in-situ hybridization for immunoglobulin mRNA with identification of light chain restriction [2].

**Extranodal NK/T Cell Lymphoma (Nasal-Type)**

The second most common malignancy of the sinonasal tract following SCC is malignant lymphoma; particularly extranodal NK/T cell lymphoma which frequently affects Asian and Latin American populations [13]. Necrosis, vascular invasion/destruction, and pseudoepitheliomatous hyperplasia are common. The latter may be mistaken for well differentiated SCC. Because extranodal NK/T cell lymphoma may also be accompanied by a significant inflammatory infiltrate, it can also be confused Wegener's granulomatosis and infectious disorders [25]. Demonstration of the EBV virus (present in nearly all cases) by in situ
hybridization for EBV-encoded early RNAs (EBER) in addition to a NK-cell immunophenotype (CD2+, CD3-, CD3e +, CD56+, CD43+, perforin and granzyme B+) is indicative of this aggressive malignancy.

**Conclusions**

Malignancies arising in the nasal cavity and paranasal sinuses are heterogeneous. Accurate classification of sinonasal SRBCTs may be challenging due to overlapping clinical, radiographic and/or histopathologic features. Diagnosis may be further complicated if the biopsy material is limited in size or is of suboptimal quality. Advances in immunohistochemistry and molecular genetics have greatly assisted in these difficult differential diagnoses. Establishing a precise diagnosis is important not only in determining how aggressive the tumor might be, but is especially critical in identifying the type of treatment needed. Moreover, a careful review with the treating clinician is vital in further enhancing accuracy.

**Acknowledgments**

The author would like to thank Cheryl Putnam and Kimberly Christian for their secretarial assistance. The author would like to also thank Drs. Rodney McComb, Sonny Johansson, William West, Douglas Gnepp, and Dennis Weisenburger for their contributions and suggestions.

**References**


22. Sumegi J, Streblow R, Frayer RW, et al. Recurrent t(2;2)(p23;q35) and t(2;8)(q35;q13) translocations, in ARMS subset without the canonical PAX3-FKHR juxtaposition, fuse PAX3 to members of the nuclear receptor transcriptional co-activator (NCOA) family of genes. Genes Chromosomes Cancer. In Press.


<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age (yrs)/Location</th>
<th>Histopathology/Architecture</th>
<th>Mitotic Activity/Necrosis</th>
<th>Cytomorphology</th>
<th>Anaplasia or Marked Atypia</th>
<th>Cytogenetic/ Molecular</th>
<th>Immunohistochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Malignant Epithelial Sinonasal Small Round Blue Cell Tumors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small cell carcinoma neuroendocrine type</td>
<td>26-77/ superior or posterior nasal cavity, maxillary, ethmoid sinuses</td>
<td>Sheets, ribbons or nests of closely packed cells with molding</td>
<td>frequent/common</td>
<td>Monotonous, small sized cells with hyperchromatic nuclei, inconspicuous or absent nuclei, and minimal cytoplasm</td>
<td>variable</td>
<td></td>
<td>CD56, Cytokeratin (punctate perinuclear), Chromogranin (variable), NSE (variable), Synaptophysin (variable), TTF-1 (variable)</td>
</tr>
<tr>
<td>Sinonasal undifferentiated carcinoma</td>
<td>20-80/ nasal cavity, maxillary antrum, ethmoid sinuses, often with extension into adjacent sites</td>
<td>Tumor cells may be arranged in nests, lobules, trabeculae or sheets</td>
<td>frequent/common</td>
<td>Medium sized nuclei with prominent nuclei surrounded by scant eosinophilic cytoplasm</td>
<td>Common</td>
<td>No recurrent cytogenetic change</td>
<td>Pankeratin, CK7, CK8, CK19, Ki-67 (most cells, variable intensity), NSE (occasional), EMA (occasional), CD99 (rare), Synaptophysin (rare), S 100 (rare), Chromogranin (rare)</td>
</tr>
<tr>
<td>Squamous cell carcinoma (non-keratinizing)</td>
<td>55–65/maxillary sinus, nasal cavity, ethmoid sinus, sphenoid and frontal sinuses</td>
<td>Ribbons, nests or strands; underlying tissue invasion often features well delineated border.</td>
<td>variable/limited</td>
<td>Poorly differentiated form most difficult to distinguish from other undifferentiated, small round cell tumors such as neuroendocrine carcinoma or olfactory neuroblastoma</td>
<td>common</td>
<td></td>
<td>Pankeratin, EMA, CK5/6, CK8, CK13, CK14, CK19</td>
</tr>
<tr>
<td><strong>Neuroectodermal Sinonasal Small Round Blue Cell Tumors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ewing sarcoma/ primitive neuroectodermal tumor (PNET)</td>
<td>&lt;30/maxillary sinus, nasal fossa</td>
<td>Sheets, lobules (less commonly cords or trabeculae- may cause dx difficulty with carcinoid or undiff carcinoma) of uniformly round cells; + Homer Wright rosettes</td>
<td>variable/common</td>
<td>Small to intermediate sized cells with poorly defined, scant or vacuolated cytoplasm and round nuclei with fine chromatin.</td>
<td>infrequent</td>
<td>t(11;22)(q24;q12) EWSR1-FLI1 (~95%) t(21;22)(q22;q12) EWSR1-ERG (~5%) Other EWSR1 or FUS variants (&lt;5%)</td>
<td>CD99 (membranous pattern), Vimentin, FLI1, NSE (variable), Synaptophysin (variable), AE1/AE3 and CAM5.2 (occasional)</td>
</tr>
<tr>
<td>Mucosal Malignant Melanoma</td>
<td>40-70/ nasal septum, paranasal sinuses (particularly maxillary)</td>
<td>Commonly deeply infiltrative with ulceration and frequent pseudopapillary architecture.</td>
<td>frequent/common</td>
<td>Amelanotic small round cell or larger melanotic epithelioid or spindle-shaped cells. Nuclear molding and/or prominent eosinophilic nuclei may be present.</td>
<td>common</td>
<td>CDKN2A/p16 (9p21) PTEN (10q23) 1q+,6p+,8q+</td>
<td>S-100, Vimentin, HMB45 (usually), Melan-A (usually), Microphthalmia transcription factor (variable), Tyrosinase (variable)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Age (yrs)/ Location</td>
<td>Histopathology/Architecture</td>
<td>Mitotic Activity/ Necrosis</td>
<td>Cytomorphology</td>
<td>Anaplasia or Marked Atypia</td>
<td>Cytogenetic/ Molecular</td>
<td>Immunohistochemistry</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>---------------------</td>
<td>-------------------------------------------------------------------------------------------</td>
<td>--------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>---------------------------</td>
<td>------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------</td>
</tr>
<tr>
<td>Olfactory neuroblastoma</td>
<td>Broad age range (&lt;10 to &gt;80) / roof of nasal cavity, cribiform plate</td>
<td>Localized to submucosa; lobular to solid growth pattern in higher grade neoplasms. Rosettes (Homer Wright and Flexner-Wintersteiner) may be present.</td>
<td>variable/variable</td>
<td>Uniformly, small sized cells with scant cytoplasm and round nuclei with fine to coarse granular chromatin and occasional small nucleoli (grade dependent).</td>
<td>variable (more common in high grade tumors)</td>
<td>Complex with aCGH studies demonstrating gain of 13q, 20q and loss of Xp as most frequent in high stage tumors.</td>
<td>Neuron specific enolase CD56 Synaptophysin (usually) S-100 protein (supporting sustentacular cells) CD57 (Leu7) (variable) Chromogranin (variable) GFAP (variable) Keratin (occasional)</td>
</tr>
<tr>
<td>Mesenchymal Sinonasal Small Round Blue Cell Tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desmoplastic small round blue cell (DSRCT)</td>
<td>15-35/sinonasal case report</td>
<td>Nests of undifferentiated cells embedded in a prominent desmoplastic stroma.</td>
<td>frequent/common</td>
<td>Small, round-oval cells with scant-moderate cytoplasm and hyperchromatic nuclei with inconspicuous nucleoli. Intracytoplasmic inclusions or vacuoles may be seen.</td>
<td>infrequent</td>
<td>t(11;22)(p13;q12) EWSR1-WT1</td>
<td>Desmin (perinuclear dot-like pattern) Pankeratin, EMA, AE1/AE3, CAM5.2 Vimentin WT1 NSE (usually) CD57 (usually) Synaptophysin (occasional) CD99 (occasional)</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>&lt;20 yr/ nasopharynx sinonasal tract</td>
<td>Embryonal subtype (ERMS): alternating hyper- and hypocellular areas with myxoid or sparsely collagenized stroma Alveolar subtype (ARMS): collagenous fibrous septa separate nests of tumor cells with loss of central cohesion Solid ARMS: sheets of tumor cells without fibrous septa</td>
<td>variable/limited</td>
<td>Small round cells with scant cytoplasm + scattered cells with eosinophilic cytoplasm and cross striations</td>
<td>common</td>
<td>ERMS: gain of all or portions of chromosomes 2, 7, 8, 11, 12, 13 and/or 20 with or without loss of 11p15 LOH ARMS: t(2;13)(q35;q14) PAX3-FOXO1 (50-60%) t(1;13)(p36;q14) PAX7-FOXO1 (~20%) Other PAX3 variants (&lt;1%) Fusion neg. (20-30%)</td>
<td>Desmin Myogenin (nuclear) myo-D1 (nuclear) Myoglobin (cytoplasmic) Vimentin (usually) CD56 (usually) Myosin (variable)</td>
</tr>
<tr>
<td>Synovial sarcoma (poorly differentiated)</td>
<td>&lt;50/maxillary, sphenoid, ethmoid and frontal sinuses</td>
<td>Often solidly packed small round cells with richly vascular hemangiopericytoma like pattern. May be focal within a typical biphasic or monophasic synovial sarcoma or it may represent the predominant pattern. Other poorly differentiated forms include large (epithelioid) cell and high-grade spindle cell.</td>
<td>variable/variable</td>
<td>Poorly differentiated small cell pattern composed of small sized cells with high nuclear to cytoplasmic ratios may be exceedingly difficult to distinguish from other small round cell tumors</td>
<td>infrequent</td>
<td>t(X;18)(p11.2;q11.2) SYT-SSX1 or SYT-SSX2 (&gt;99%)</td>
<td>EMA BCL2 TLE1 Cytokeratin (variable) CD99 (variable) S-100 (occasional) Vimentin (spindle cells only)</td>
</tr>
</tbody>
</table>
### Hematolymphoid Sinonasal Small Round Blue Cell Tumors

<table>
<thead>
<tr>
<th></th>
<th>Extraduillary plasmacytoma</th>
<th>Extramedullary plasmacytoma</th>
<th>Extranodal NK/T cell lymphoma, nasal</th>
</tr>
</thead>
<tbody>
<tr>
<td>35-75/ nasal cavity, paranasal sinuses</td>
<td>Diffuse infiltrate of uniform (well-differentiated) to pleomorphic (anaplastic) neoplastic plasma cells. Amyloid deposits (11-38%)</td>
<td>Variable/uncommon Diffuse infiltrate of uniform (well-differentiated) to pleomorphic (anaplastic) neoplastic plasma cells. Amyloid deposits (11-38%)</td>
<td>Small to large (well to poorly differentiated) cells with fine to coarse nuclear chromatin and prominent nucleoli. Intracytoplasmic crystals, Dutcher bodies, and perinuclear hof may be present. Occasionally 14q32 (IGH) [although in contrast to multiple myeloma lacks the t(11;14), -13 or 13q-] Light chain restriction CD138 CD38 CD45 VS38 EMA (variable) CD79a (variable) CD31 (occasional) CD56 (occasional)</td>
</tr>
<tr>
<td>50-75/nasal cavity, paranasal sinuses, nasopharynx</td>
<td>Diffuse neoplastic lymphoid proliferation with angiocentric/angiodestructive growth pattern, mucosal ulceration, pseudoepitheliomatous hyperplasia and frequent associated inflammatory infiltrate.</td>
<td>Frequent/common Small or medium-sized cells to large transformed cells with round, oval or irregular nuclei and azurophilic cytoplasmic granules. Common del(6)(q21-25) i(6)(p10) EBV (ISH) 10% with T cell receptor gene rearrangement, no immunoglobulin light or heavy chain rearrangements</td>
<td>CD2 CD3e (cytoplasmic) Granzyme B Perforin CD45 CD56 (cytoplasmic) (usually) TIA-1 (usually)</td>
</tr>
</tbody>
</table>

1Finke NM et al. [18]
Table 2. Cytokeratin Expression in Sinonasal Poorly Differentiated Squamous Cell Carcinoma (SCC), Nonkeratinizing Squamous Cell Carcinoma (NKSCC), and Sinonasal Undifferentiated Carcinoma (SNUC)*

<table>
<thead>
<tr>
<th></th>
<th>CK4</th>
<th>CK5/6</th>
<th>CK7</th>
<th>CK8</th>
<th>CK10</th>
<th>CK13</th>
<th>CK14</th>
<th>CK19</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCC</td>
<td>+ (3/10)</td>
<td>+ (9/10)</td>
<td>+ (6/10)</td>
<td>+ (9/10)</td>
<td>-</td>
<td>+ (9/10)</td>
<td>+ (8/10)</td>
<td>+ (9/10)</td>
</tr>
<tr>
<td>NKSCC</td>
<td>-</td>
<td>+ (9/10)</td>
<td>-</td>
<td>+ (9/10)</td>
<td>-</td>
<td>+ (8/10)</td>
<td>+ (8/10)</td>
<td>+ (9/10)</td>
</tr>
<tr>
<td>SNUC</td>
<td>-</td>
<td>-</td>
<td>+ (3/6)</td>
<td>+ (6/6)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+ (3/6)</td>
</tr>
</tbody>
</table>

*From Franchi et al.3
Slide 1

North American Society of Head and Neck Pathology
The Small Round Blue Cell Tumors of the Sinonasal Area

Julia A. Bridge, M.D. FACMG
University of Nebraska Medical Center

Slide 2

Diagnostic Classification is Challenging

- Rare (nasal cavity and paranasal sinus malignancies comprise 0.2-0.8 percent of all malignancies)
- Diverse origin (epithelial, hematolymphoid, neuroectodermal, mesenchymal)
- Small-sized biopsy sample
- Atypical clinical presentation (unusual age group or anatomic location may further complicate the differential dx)

Slide 3

Sinonasal Small Round Blue Cell Tumors
Overlapping radiographic and histopathologic features
Slide 4

Establishing an accurate diagnosis often requires studies beyond routine hematoxylin and eosin-stained sections

Slide 5

Immunohistochemical features are helpful, but sometimes absent in poorly differentiated tumors

Slide 6
Cytogenetic/molecular techniques may be helpful in the differential diagnosis of sinonasal SRBCTs.

- t(11;22)(p13;q12) EWSR1-WT1
- 100 bp
- PAX7-FOXO1
- PAX3-FOXO1
- neg. control
- 22q12 (EWSR1)

Overview: Emphasis placed on differential dx of these sinonasal SRBCTs and use of ancillary studies in their diagnostic management.

<table>
<thead>
<tr>
<th>Epithelial</th>
<th>Neuroectodermal</th>
<th>Mesenchymal</th>
<th>Hematolymphoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell carcinoma neuroendocrine type</td>
<td>Ewing’s sarcoma/ peripheral primitive neuroectodermal tumor (pPNET)</td>
<td>Desmoplastic Small Round Cell Tumor (DSRCT)</td>
<td>Extramedullary Plasmacytoma</td>
</tr>
<tr>
<td>Sinonasal undifferentiated carcinoma</td>
<td>Masculin Malgnant Melanoma</td>
<td>Rhabdomyosarcoma</td>
<td>Extramedullary NK/T cell lymphoma, nasal</td>
</tr>
<tr>
<td>Squamous cell carcinoma (nonkeratinizing)</td>
<td>Oligo/ Neuroblastoma</td>
<td>Synovial Sarcoma (poorly differentiated)</td>
<td></td>
</tr>
</tbody>
</table>

**Squamous Cell Carcinoma**

**Macroscopy:** exophytic, papillary, friable, hemorrhagic, indurated

**Clinical Features:** chronic sinusitis-like symptoms, proptosis, diplopia or lacrimation (advanced cases); CT/MRI – bony invasion, disease extension such as to the orbit

**Histopathology:** poorly differentiated, non-keratinizing may exhibit features overlapping with other SRBCTs
Slide 10

NUT midline carcinoma

NUT Midline Carcinoma

• undifferentiated carcinoma, often with focal squamous differentiation that may arise in the sinonasal area of children and adults
• striking histologic overlap with NUTwt SCC

Sinonasal Basaloid SCC

Wieneke, JA et al. Cancer 85:841-54, 1999

Slide 11

NUT Midline Carcinoma

• In two-thirds of cases -
NUT (nuclear protein in testis) localized to 15q14 is fused to BRD4 (bromodomain-containing protein 4) on 19p13

\[ t(15;19)(q14;p13) \]

Slide 12

NUT-BRD4 Dual Color, Dual Fusion Probe

Spanning 15q14 (NUT)

Spanning 19p13 (BRD4)
Slide 13

*NUT Midline Carcinoma*

- In remaining 1/3 of cases, the NUT translocation partner is not BRD4 ("NUT-variant cases")

- Foci of abrupt keratinization in an otherwise undifferentiated carcinoma are especially prominent in the NUT-variant cases and the average survival also appears to be longer

---

Slide 14

*NUT Break-Apart Probe*

- Proximal to 15q14
- Distal to 15q14

---

Slide 15

*NUT Break-Apart Probe*

(allows for detection of variant translocations)
Slide 16

**BRD4-NUT Midline Carcinoma**

---

Slide 17

**IHC Pattern of NUT Midline Carcinoma vs Other Sinonasal SRBCTs**

<table>
<thead>
<tr>
<th></th>
<th>CK</th>
<th>p63</th>
<th>NUT</th>
<th>EBV S-140</th>
<th>LCA</th>
<th>CD56</th>
</tr>
</thead>
<tbody>
<tr>
<td>NUT midline carcinoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nasopharyngeal carcinoma</td>
<td>+</td>
<td>-A</td>
<td>+A</td>
<td>R+</td>
<td>-A</td>
<td>-</td>
</tr>
<tr>
<td>SCCNET</td>
<td>+A</td>
<td>-A</td>
<td>-A</td>
<td>R+</td>
<td>+A</td>
<td>-</td>
</tr>
<tr>
<td>Hematolymphoid neoplasm</td>
<td>-</td>
<td>R+</td>
<td>-</td>
<td>V</td>
<td>V</td>
<td>V</td>
</tr>
<tr>
<td>MM</td>
<td>R+</td>
<td>R+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>R+</td>
</tr>
</tbody>
</table>


---

Slide 18

**Sinonasal Undifferentiated Carcinoma**

**Clinical Features:** locally extensive disease, more common in males (3rd-9th decade), nasal obstruction, rhinorrhea, facial pain, proptosis (symptoms of relatively short duration)

---
Slide 19

**Histopathology:** nests, trabeculae or sheets of highly mitotic tumor cells; growth along mucosal surface, mucosal gland extension, ulceration and lymphovascular invasion common; prominent necrosis and apoptosis

**Differing Cytokeratin Patterns**

<table>
<thead>
<tr>
<th></th>
<th>CK4</th>
<th>CK5/6</th>
<th>CK7</th>
<th>CK8</th>
<th>CK10</th>
<th>CK13</th>
<th>CK14</th>
<th>CK19</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCC</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>(3/6)</td>
<td>(6/10)</td>
<td>(9/10)</td>
<td>(9/10)</td>
<td>(9/10)</td>
<td>(9/10)</td>
<td>(9/10)</td>
<td>(9/10)</td>
<td>(9/10)</td>
</tr>
<tr>
<td>NKSCC</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>(9/10)</td>
<td>(9/10)</td>
<td>(9/10)</td>
<td>(9/10)</td>
<td>(9/10)</td>
<td>(9/10)</td>
<td>(9/10)</td>
<td>(9/10)</td>
<td>(9/10)</td>
</tr>
<tr>
<td>SNUC</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>


Differing Cytokeratin Patterns

SCC vs NKSCC vs SNUC

Slide 20

**Small Cell Carcinoma, Neuroendocrine Type**

**Clinical Features:**
- mean age of 50 yrs
- superior/posterior nasal cavity followed by maxillary or ethmoid sinuses
- advanced tumors invade skull base, orbit or brain
- epistaxis, nasal obstruction, and facial pain or mass
**Slide 22**

**Histopathology:** Closely packed tumor cells with dense chromatin, absent nucleoli and minimal cytoplasm; necrosis and crush artifact common.

**Slide 23**

**Crush Artifact:** Not confined to small cell neuroendocrine carcinoma as evidenced in this olfactory neuroblastoma.

**Slide 24**

**Immunohistochemistry**

**SCCNET** – shows variable reactivity for:
- Cytokeratin (punctate, paranuclear or globoid pattern)
- Chromogranin
- Synaptophysin
- NSE (usually focal)
- S-100 protein (dispersed)
- Thyroid transcription factor-1 (TTF-1)

**ONB** – shows variable reactivity for:
- Cytokeratin (usually negative)
- Chromogranin
- Synaptophysin
- NSE (usually diffuse)
- S-100 protein (sustentacular)
- Thyroid transcription factor-1 (negative)
**Olfactory Neuroblastoma**

**Localization:** arises from specialized olfactory epithelium - cribiform plate, superior turbinate and superior 1/3 of nasal septum

**Clinical Features:** bimodal age distribution (2nd and 6th decades); unilateral nasal obstruction, epistaxis, headache; locoregional recurrences are common

---

**Histopathology:** distinct lobular pattern, neuronal processes, Homer Wright and Flexner-Wintersteiner rosettes, sustentacular cells (S-100 positive)

---

**Mucosal Malignant Melanoma**

**Clinical Features:** older pts (5-8th decade); usually arises in anterior nasal cavity/septum/lower or middle turbinates with concomitant nasal symptoms (ie. nasal obstruction, epistaxis, discharge…)

**Macroscopy:** large, bulky, polypoid, variable melanin production resulting in tan, black or brown cut surface
Undifferentiated (small to medium cell), epithelioid, spindled, plasmacytoid, and/or rhabdoid cells; melanin pigment detectable by light microscopy in ~2/3 of cases.

Round Cell Neoplasms

- The defining feature for some round cell tumors, such as Ewing’s sarcoma, is the presence of a nonrandom translocation leading to the fusion of certain genes.

Round Cell Neoplasms

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Translocation</th>
<th>Gene Fusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ewing’s sarcoma/ pPNET</td>
<td>t(11;22)(q12;q12)</td>
<td>EWSR1-FLI1</td>
</tr>
<tr>
<td>Alveolar rhabdomyosarcoma</td>
<td>t(2;13)(p11;q14)</td>
<td>PAX3-FOXO1</td>
</tr>
<tr>
<td>Desmoplastic small round-cell tumor</td>
<td>t(11;22)(q13;q12)</td>
<td>EWSR1-WT1</td>
</tr>
<tr>
<td>Round cell liposarcoma</td>
<td>t(12;16)(q13;p11)</td>
<td>FUS-CHOP</td>
</tr>
<tr>
<td>Poorly differentiated synovial sarcoma</td>
<td>t(X;18)(p11.2;q11.2)</td>
<td>SYT-SSX1 SYT-SSX2</td>
</tr>
</tbody>
</table>
**Ewing’s Sarcoma/pPNET**

**Clinical Features:**
- younger pt (<30 yrs);
- usually arises in maxillary sinus and nasal fossa; pain, mass and obstruction

**Macroscopy:** smaller in size than if arising in other sites

---

**Ewing’s Sarcoma/pPNET**

CD99

---

**t(11;22)(q24;q12) can be detected by:**

- Conventional Cytogenetics
- FISH
- RT-PCR
Rhabdomyosarcoma

Clinical Features:
ERMS
• children & adolescents

ARMS
• pts. slightly older than ERMS

ERMS and ARMS
• nasal cavity, nasopharynx, ethmoid sinus, maxillary sinus
• may appear as polyoid sinonasal mass or protruding gelatinous mass

Histopathology

ERMS
• Alternating cellular and myxoid areas

ARMS
• “Alveolar” growth pattern

myogenin
desmin

Frozen Section:
• Malignant undifferentiated neoplasm, favor small cell carcinoma

76 year old female

• New onset of left ptosis, dysarthria, and headache (bilateral temporal)
• Increasing problems with vision
• Admitted for suspected cerebrovascular accident

Frozen Section:
• Malignant undifferentiated neoplasm, favor small cell carcinoma
Small round cell neoplasm with variable crush artifact

Battery of immunostains all negative except:
- EMA
- MAK6
- AE1/AE3
- CK7
- CAM5.2
- Chromogranin
- Synaptophysin
- GFAP
- S-100 protein
- Melan-A
- CD45
- Epstein-Barr viral LMP
- Myeloperoxidase

Supernatant Harvest
(1st change of culture media 24 to 48 hours within specimen receipt)
Slide 43

**ARMS characteristic**
\[ t(2;13)(q35;q14) \] identified

<table>
<thead>
<tr>
<th>Cell 1</th>
<th>Cell 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="cell1.png" alt="Image" /></td>
<td><img src="cell2.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Chromosomes

Slide 44

**Subsequent Immunophenotype**

- IHC revealed strong, diffuse nuclear positivity for MyoD1 and myogenin and cytoplasmic staining for desmin and muscle-specific actin

Slide 45

**Alveolar Rhabdomyosarcoma**

- 70-80% are fusion +
- 20-30% are fusion negative

- Majority: \( t(2;13)(q35;q14) \)
- Minority: \( t(1;13)(q36.1;q14) \)

- \( 2 \) and \( 13 \)
Slide 46

61 year old male

- Large mass involving the paranasal sinuses with extension into the nasopharynx & adjacent orbit
- Sheets and nests of small undifferentiated cells admixed with slightly larger cells exhibiting relatively abundant clear cytoplasm
- CD56, cytokeratin, and synaptophysin positive

Douglas R. Gnepp, M.D. Rhode Island Hospital

Cytokeratin
Synaptophysin

Slide 47

Exhibited a PAX7-FOXO1 fusion transcript

CASE 1             CASE 2             CASE 3               CASE 4
Exhibited a PAX7-FOXO1 fusion transcript

Slide 48

Diagnosis of head/neck ARMS in older adults

- Is complicated by its rarity, lack of an alveolar pattern, and a potentially misleading immunoprofile (CD56, cytokeratin and synaptophysin immunoreactivity) if myogenic markers are not employed
Slide 49

"Fusion Negative" ARMS
PAX3-NCOA1 or PAX3-NCOA2

Slide 50

Cytology Preparations

Slide 51

PAX3-FOXO1 positive

M = 100 bp ladder
Lane 1 = pt. sample
Lane 2 = PAX3-FOXO1 positive control
Lane 3 = negative control
Embryonal Rhabdomyosarcoma

- Unlike ARMS, a tumor-specific translocation has not been identified for ERMS
- However, a recurrent pattern of chromosomal imbalances is seen in ERMS that may contribute to its accurate nosology

Slide 53

52,X,-X,+2,+8,+12,+13,+13,+15,+20

Slide 54

Embryonal Rhabdomyosarcoma
Loss of Heterozygosity (11p15)
Slide 55

**Lymphoma**

- Second most common malignancy of sinonasal tract (B-cell, T-cell or nasal-type NK/T-cell) following squamous cell carcinoma

Slide 56

Slide 57

**Extranodal NK/T-Cell Lymphoma (Nasal Type)**

- Frequent in Asian and Latin American populations
- Neoplastic cells may be small and/or medium-sized; vascular invasion/destruction, necrosis, and inflammatory infiltrate common
**Slide 58**

**Epstein Barr Virus (EBV)-encoded RNAs (EBER) ISH**

- In situ hybridization for Epstein-Barr virus (EBV)-encoded RNAs (EBER, small nonpolyadenylated RNA) is a highly sensitive technique for demonstration of EBV.
- EBV present in nearly all extranodal NK/T cell lymphomas.
- CD2+, CD3-, CD3e+, CD56+, CD43+, perforin and granzyme B+.

**Slide 59**

**Summary**

- Nasal cavity/paranasal sinus SRBCTs are heterogeneous.
- Accurate classification may be challenging due to overlapping clinical, radiographic and/or histologic features.
- Small or suboptimal biopsy material may further complicate diagnosis.
- Advances in immunohistochemistry and molecular genetics have greatly assisted in these difficult differential diagnoses.