Biphenotypic Sinonasal Sarcoma
A Review and Update

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Context.—Biphenotypic sinonasal sarcoma (BSNS) is a rare, slow-growing soft tissue sarcoma of the sinonasal tract, typically presenting with nonspecific obstructive nasal symptoms. Although recurrences are common, no metastases have been reported, and only 1 patient has died of disease thus far. It characteristically demonstrates rearrangements of PAX3 with multiple fusion partners, the most common of which is MAML3.

Objectives.—To highlight the most important diagnostic features, including morphologic, immunohistochemical, and molecular findings, and to provide comparisons to other entities in the differential diagnosis. We also aim to provide a summary of the clinical features and outcomes in cases reported to date.

Data Sources.—Recently published literature encompassing BSNS and its synonym, low-grade sinonasal sarcoma with neural and myogenic differentiation.

Conclusions.—BSNS is a sinonasal tumor that is important to recognize because its biologic behavior differs from most of the entities in the differential diagnosis. The diagnosis can typically be rendered through a combination of morphology, immunohistochemical stains, and ancillary testing for characteristic PAX3 rearrangements.


Biphenotypic sinonasal sarcoma (BSNS) is a rare low-grade sarcoma first described by Lewis et al1 in 2012 as low-grade sinonasal sarcoma with neural and myogenic differentiation. The authors described 28 cases of an infiltrative, cellular spindle cell neoplasm with uniform nuclear features, which were negative for synovial sarcoma fusion transcripts. Commensurate with many other neoplastic entities first described in the 21st century,2 it is difficult to separate the discovery of BSNS from its genetic characterization. Cytogenetics was performed on 2 of the cases in the initial series, which both showed a t(2;4) translocation. Subsequent transcriptome analysis performed on 1 of the tumors with a t(2;4) translocation revealed a fusion transcript of exons 1 to 7 of PAX3 on chromosome 2, to exons 2 to 5 of MAML3 on chromosome 4.3 Additional fluorescence in situ hybridization and reverse transcriptase–polymerase chain reaction studies confirmed a rearrangement of PAX3 in 24 of 25 tumors, with a resulting PAX3-MAML fusion gene in 19 of 25 tumors (Table). This fusion results in retention of the DNA-binding domains of PAX3 with loss of the Notch-binding domain of MAML3, and the same authors4 found that PAX3-driven reporter activity was markedly increased in an experimental model using a mammalian vector with a PAX3-MAML3 cDNA sequence inserted. The resulting PAX3-MAML3 fusion protein has a function similar to that of the PAX3-FOXO1 fusion protein described in alveolar rhabdomyosarcoma. In fact, a similar PAX3-FOXO1 fusion has been subsequently described in BSNS, in addition to PAX3-NCOA1 fusions and PAX3 rearrangements with as yet unknown partners.4–6

The name of BSNS and its original name, low-grade sinonasal sarcoma with neural and myogenic differentiation, stem from its expression of markers of both neural crest and skeletal muscle differentiation.1 The discovery of recurrent PAX3 alterations provides insight into its line of differentiation, in addition to its oncogenesis, as PAX3 is known to be a transcription factor involved in the development of skeletal muscle and tissues derived from neural crest cells.7,8 Additionally, the conserved site of origin in the nasal cavities and local tissues is explained by its link to PAX3 activity, since this transcription factor has been described to be an important promotor of nasal structure development.9

Epidemiology and Clinical Features

Biphenotypic sinonasal sarcoma primarily affects adults, with reported cases observed in patients ranging from ages 24 to 87 years (mean, 50–51 years).1,3,5,6,10 It has a predilection for women, with a female to male ratio of 2:1. Patients typically present with nonspecific symptoms of nasal passage obstruction, including difficulty with nasal breathing, epistaxis, and nasal and sinus pain and congestion. Biphenotypic sinonasal sarcoma typically involves multiple sinonasal subsites, with the superior nasal cavity and ethmoid sinus most commonly involved, followed by the sphenoid sinus. The tumors are commonly large,
measuring an average of approximately 4 cm in greatest
dimension, and can be locally destructive. Invasion beyond
the nasal cavity and sinuses may occur, with extension into
the orbit in 25% of cases (requiring orbital exenteration) and
through the cribriform plate in 10% of cases.

**HISTOPATHOLOGY**

Histologically, BSNS consists of an infiltrative, highly cellular
spindle cell proliferation of uniform, low-grade spindle cells arranged in medium to long fascicles (Figure 1, A), with occasional herringbone pattern observed (Figure 1, B). The spindled cells are long and slender, with syncytial cytoplasmic borders, and feature nuclei with vesicular chromatin and tapered, rather than blunted, nuclear tips. Mitotic activity is very low, usually less than 1 mitosis per 10

Histologic examination of BSNS shows nuclear-cytologic
staghorn hemangiopericytoma-like vessels are a common
feature, bringing solitary fibrous tumors (SFTs) and glo-

mangiopericytomas into the differential diagnosis. Micro-

scopic invasion into adjacent bone is seen in approximately
20% of cases (Figure 1, D), and it highlights the locally
aggressive nature of this entity.11

Rhabdomyoblastic differentiation has been described in
approximately 10% of cases and is seen either as a
morphologic hematoxylin eosin finding or exclusively
immunohistochemically, in the form of variable desmin,
myoD1, and myogenin expression. Rhabdomyoblastic dif-
ferentiation is particularly associated with alternate
PAX3 fusion partners FOXO1 and NCOA1.4–6,12 However, cases with the more common PAX3-MAML3 gene fusion have also been reported to express skeletal muscle markers myogenin and myoD1, so expression of these markers is not specific for alternate PAX3 fusion partners.8 Because of the low number of reported cases and lack of available clinical follow-up, it remains to be seen if rhabdomyoblastic differentiation or the presence of any particular alternate fusion partners portends a greater or lesser degree of aggressive behavior.

**IMMUNOHISTOCHEMISTRY**

A diagnosis of BSNS requires knowledge and a high index of suspicion of this rare entity when encountering a spindle cell neoplasm with low-grade cytologic features arising in proximity to the nasal sinuses or passages, and it is best

confirmed by break-apart fluorescence in situ hybridization assay for rearrangements of PAX3. This assay, however, remains limited to a few research and reference laboratories at the time of this publication. Thus, a panel of more readily accessible immunohistochemical stains that could distinguish BSNS from tumors with similar histologies is desirable.

Based on initial reports,4,5,10 a panel has been proposed by
Rooper et al11 that includes S100, SOX10, smooth muscle
actin, calponin, myogenin, β-catenin, factor XIIIa, and
cytokeratin (Figure 2). Thus far, nearly all reported
BSNSs show at least focal S100 (focal defined as less than
10% expression),6,11 a marker of neural crest origin.

Expression of smooth muscle markers actin and calponin
is nearly universal as well, although diffuse expression is
only reported in approximately 50% of tumors, with a large
subset of tumors only showing focal staining. They can also
show variable expression of desmin, myogenin, and factor
XIIIa, while they are negative for cytokeratin and SOX10.

The latter stains are helpful in differentiating from synovial sarcomas, the vast majority of which exhibit at least focal
keratin expression,13 as well as separating from neural-
derived tumors, including schwannomas and malignant
peripheral nerve sheath tumors (MPNSTs), most of which
will show at least focal SOX10 expression.14 Nuclear β-
catenin expression has also been purported to be a useful
diagnostic adjunct, as at least focal nuclear β-catenin
expression has been reported in 12 of 13 cases.4,10,11
However, nuclear β-catenin expression is a well-character-
ized feature of glomangiopericytomas, and it has been
reported in large subsets of synovial sarcomas and SFTs
(28% and 40%, respectively).15,16 These tumors are all within
the morphologic differential diagnosis in sinonasal sites,
making it somewhat less useful. Thus, based on existing
data, a combined expression of S100 and either actin
or calponin, in the absence of SOX-10 and cytokeratin
expression, should be sufficient for a diagnosis of most
BSNSs. Fluorescence in situ hybridization interrogation for
PAX3 rearrangements can be reserved for atypical cases
that do not fit this immunoprofile and for which morphology is
not typical.

**PROGNOSIS AND TREATMENT**

Biphenotypic sinonasal sarcomas are treated by local excision, with or without adjuvant radiation treatment. Few
cases of adjuvant radiation treatment have been reported,
and even fewer with adjuvant chemotherapy; thus, the
efficacy of adjuvant therapy versus re-excision is unknown.5

The recurrence rate is approximately 40% to 50%, with
disease recurrence-free intervals ranging from less than 1
year to more than 9 years. No regional metastasis or distant
metastases have yet been reported. Overall, disease-related

### List of Cases of Biphenotypic Sinonasal Sarcoma With Reported Genetic Alterations

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Reported Cases, No.</th>
<th>PAX3-MAML3, No.</th>
<th>PAX3-FOXO1, No.</th>
<th>PAX3-NCOA1, No.</th>
<th>PAX3-Unknown Partner, No.</th>
<th>MAML3 Without PAX3, No.</th>
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<td>25</td>
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<td>6</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
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<tr>
<td>Fritchie et al, 2016</td>
<td>44</td>
<td>24</td>
<td>3</td>
<td>1</td>
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Four cases from Rooper et al were previously reported in Huang et al. An unknown number of cases from Fritchie et al were previously reported in Wang et al. Because of overlapping cases among cohorts, totals are not provided.
mortality is very limited, with only 1 reported case of death due to disease. However, the prognostic data are limited by a large proportion of cases reported without clinical follow-up. Of note, with available data, the prognosis of BSNS is significantly better than alveolar rhabdomyosarcomas with the same $\text{PAX3-FOXO1}$ gene fusion. This finding highlights the importance of the cell of origin in the oncogenesis of different entities with recurrent gene fusions, a concept perhaps best illustrated by the recurrent $\text{ETV6-NTRK3}$ gene fusions across biologically distinct tumors of epithelial, mesenchymal, and hematopoietic differentiation (secretory carcinoma, infantile fibrosarcoma, and acute myeloid leukemia, respectively).

### DIFFERENTIAL DIAGNOSIS

Levis et al postulated that prior to its description, BSNS was probably most commonly diagnosed as a low-grade fibrosarcoma or low-grade peripheral nerve sheath tumor. With the expanded diagnostic repertoire of soft tissue sarcomas based on cytogenetic and molecular characterization, fibrosarcoma has largely fallen out of favor as a diagnostic term, and today the entities most closely related morphologically and immunophenotypically are synovial sarcomas and malignant peripheral nerve sheath tumors.

Synovial sarcomas are similarly composed of densely cellular fascicles of spindled cells with indistinct cell borders, overlapping nuclei, and soft, evenly dispersed chromatin (Figure 3, A). Mitotic activity is one of the best distinguishing factors, as synovial sarcomas should have significantly higher mitotic activity than BSNS, with some large series showing most localized synovial sarcomas to have 10 or more mitoses per 10 high-power fields. Synovial sarcomas also frequently have scattered collections of thick (“ropey”) collagen bundles and calcifications, which are not features of BSNS, and the epithelial proliferations in biphasic synovial sarcomas consist of polygonal epithelioid cells rather than entrapped well-differentiated squamous or sinonasal epithelium. Synovial sarcomas can have an immunohistochemical expression profile similar to that of BSNS, with subsets exhibiting focal expression of S100, smooth muscle actin, and myogenin, and the vast majority lacking SOX10 expression, but almost all synovial sarcomas (including monophasic and biphasic) should express cytokeratin and/or epithelial membrane antigen. Diffuse expression of TLE1 has been demonstrated to be a sensitive and specific marker for synovial sarcoma, but diffuse TLE1 expression has also been reported in a single case of BSNS with $\text{PAX3-FOXO1}$ fusion and has not been studied in the other published cohorts. Therefore, an immunohistochemical panel approach is recommended. If readily available, a negative assay for the detection of $\text{SS18-SSX}$ speaks against a synovial sarcoma, as was performed in the initial cohort of BSNS.

Also in the differential diagnosis are malignant peripheral nerve sheath tumors, including those with rhabdomyoblastic differentiation (so-called malignant triton tumors; Figure 3, B). Although MPNSTs can involve head and neck sites, sinonasal sites are very rarely involved. Many of those
reported in this region have been called low-grade MPNSTs and likely actually represent BSNS. Most MPNSTs exhibit high-grade cytologic features with frequent mitoses, as well as necrosis. Immunophenotypically, they are at least focally positive for S100, but they are typically negative for smooth muscle actin and nuclear β-catenin expression, and most also exhibit SOX10 expression. In a study by Kang et al, 32 of 48 MPNSTs were SOX10⁺, whereas only 7 of 97 synovial sarcomas exhibited SOX10 expression, and no cases of BSNS have shown SOX10 expression.

Glomangiopericytoma (sinonasal-type hemangiopericytoma) is a rare mesenchymal neoplasm consisting of bland ovoid cells with indistinct cell borders that appear more epithelioid than the cells in BSNS. Glomangiopericytomas also share the hemangiopericytoma-like vascular pattern and frequently exhibit perivascular hyalinization (Figure 3, C). Although fascicles are often seen, they are not typically as prominent as in BSNS. The cells consistently express smooth muscle markers, such as actin, and are thought to be derived from perivascular glomus-like myoid cells. They similarly exhibit nuclear β-catenin expression due to mutations in CTNNB1, but glomangiopericytomas are negative for S100.

Because of their spindled nature and hemangiopericytoma-like vasculature, sinonasal soft tissue SFTs also enter the differential diagnosis. Approximately 6% of SFTs occur in head and neck sites, of which sinonasal SFTs are the most common. Morphologically, SFTs consist of a syncytial

Figure 2. Immunohistochemical findings in biphenotypic sinonasal sarcoma (A) include positive staining with S100 (B), smooth muscle actin (C), and calponin (D), and negative staining with SOX10 (E) and cytokeratin AE1/AE3/CAM5.2 (F) (hematoxylin-eosin, original magnification ×40 [A]; original magnification ×40 [B through F]).
proliferation of bland spindled cells in a haphazard arrangement, and more specifically lack the fascicular and herringbone morphology of BSNS (Figure 3, D). Similar to BSNS and glomangiopericytomas, SFTs characteristically have hemangiopericytoma-like vasculature and a low mitotic rate. In contrast to BSNS, they often exhibit alternating hypocellular and hypercellular areas with more stromal hyalinization, and, similar to synovial sarcomas, can have thick bands of “ropey” collagen. Immunohistochemically, most SFTs exhibit diffuse CD34 expression and STAT6 expression (90% and 97%, respectively, in head and neck sites).5 The latter finding is based on a recurrent intrachromosomal rearrangement of 12q resulting in a NAB2-STAT6 fusion, and compared with other mesenchymal tumors, is highly sensitive and specific for SFT, although STAT6 has not been well studied in BSNS.33–35 In addition to STAT6, S100 and smooth muscle actin are the most helpful immunohistochemical adjuncts because SFTs rarely express these markers, particularly in concert with one another.36 As previously discussed, approximately 40% of SFTs can show nuclear β-catenin expression.16

CONCLUSIONS

Biphenotypic sinonasal sarcoma is a rare neoplastic entity, thus far reported to arise only in the nasal cavity, sinuses, and adjacent tissues. It is important to distinguish from other tumors in the morphologic differential diagnosis, which range from benign tumors (glomangiopericytoma), because of its low-grade cytologic features and low mitotic index, to aggressive tumors with high metastatic potential (synovial sarcoma) because of its high cellularity and proclivity for bone invasion. This distinction can be made with a routine immunohistochemical panel in a large subset of cases, with the option for either fluorescence in situ hybridization interrogation of PAX3 or reverse transcriptase–polymerase chain reaction of the described chimeric fusion genes as a diagnostic adjunct. Additional case series with consistent clinical follow-up are necessary to determine the biologic potential of these sarcomas, as well as to ascertain whether distinct gene fusions have any effect on prognosis and treatment.

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References


