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SPECIAL ISSUE: TOP TEN HEAD AND NECK DIFFERENTIALS

Top 10 Significant Spindled Head and Neck Lesions to Scrutinze

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Abstract

Background Spindled lesions are a challenging area in head and neck pathology. This is particularly true in the sinonasal tract, where several uncommon entities with both unique and overlapping morphologic, immunophenotypic, and/or molecular features can occur.

Methods Review.

Results The clinicopathologic characteristics of biphenotypic sinonasal sarcoma and nine important differential diagnostic considerations with one or more overlapping feature are summarized to establish a practical framework for approaching spindled lesions of the sinonasal tract.

Conclusion Morphologic evaluation is central to the work up of sinonasal spindle cell lesions–in particular, cellular morphology, tumor architecture and growth pattern, and the presence of admixed epithelial elements – however, focused immunohistochemical analysis of neural, myogenic, rhabdomyoblastic, epithelial, and/or melanocytic marker expression and/or ancillary tests for tumor-specific molecular alterations may be necessary for definitive diagnosis.

Keywords Nerve sheath tumors · Smooth muscle tumors · Rhabdomyosarcoma · Glomangiopericytoma · Solitary fibrous tumor · Synovial sarcoma

Introduction

Spindled head and neck lesions are a frequent source of consternation for general and subspecialty pathologists alike. This is particularly true in the sinonasal tract, where several uncommon entities with both unique and overlapping morphologic, immunophenotypic, and/or molecular features can occur. Herein, the clinicopathologic characteristics review of one such entity–biphenotypic sinonasal sarcoma–will be presented along with nine important differential diagnostic considerations with one or more overlapping feature to establish a practical framework for approaching spindled lesions of the sinonasal tract.

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Biphenotypic Sinonasal Sarcoma

Biphenotypic sinonasal sarcoma (BSNS)–originally termed low-grade sinonasal sarcoma with neural and myogenic features–is a rare, recently characterized low-grade sinonasal malignancy that typically occurs in middle-aged patients and shows a female sex predilection [1–3]. It usually demonstrates significant infiltration of the sinonasal mucosa and frequently involves the underlying bone. While local recurrences are common, the long-term clinical course of BSNS is usually indolent, and distant metastases have not been reported. As such, surgical excision or debulking is the main treatment for most patients; rarely, adjuvant radiation and/or chemotherapy may be necessary for aggressive cases (i.e., intracranial extension). Microscopically, BSNS is composed of infiltrative fascicles of bland-appearing spindle cells with scant eosinophilic cytoplasm and tapered nuclei (Fig. 1 and Table 1); these fascicles frequently surround and entrap benign sinonasal epithelial structures. Concordant with its low-grade clinical behavior, mitotic activity is low, and necrosis is uncommon. Furthermore, as the name indicates, tumor cells demonstrate a unique biphenotypic immunophenotype, with variable expression of neural (S100

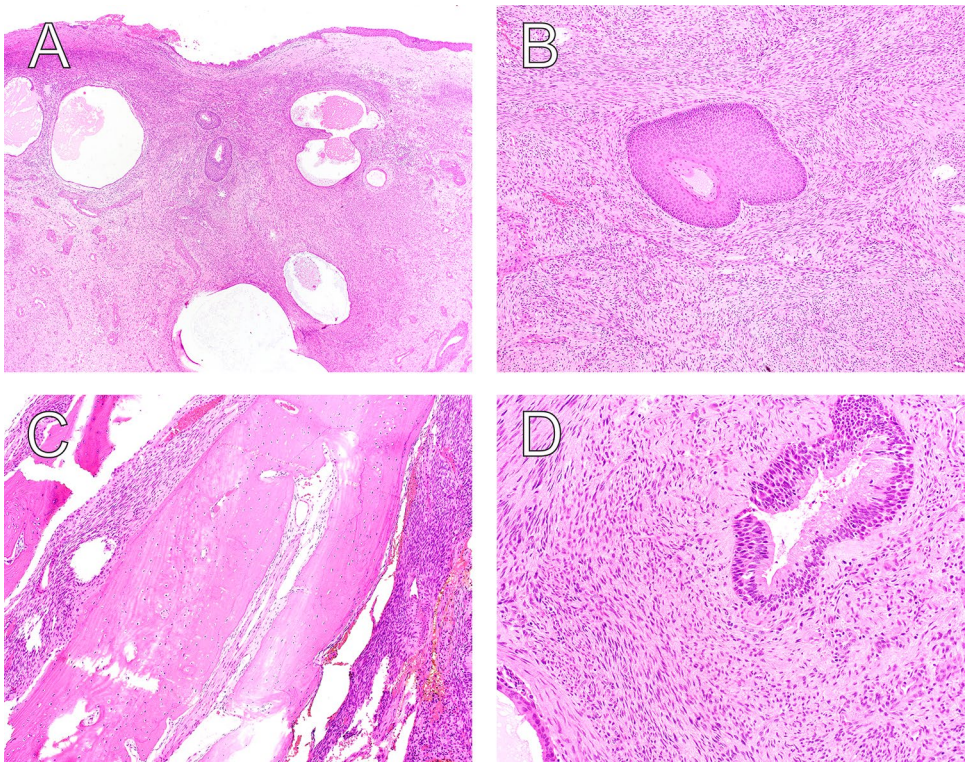

Fig. 1 Biphenotypic sinonasal sarcoma (BSNS). **A** Low-power view highlights the infiltrative nature of BSNS, with frequent entrapment of benign epithelial structures. **B**–**D** BSNS is composed of fascicles of bland-appearing spindle cells with eosinophilic cytoplasm and tapered nuclei, which permeate the subepithelial stroma and frequently involve bone (**C**). [Magnification: A = 4X; B and C = 10X; and, D = 20X]

protein) and myogenic (smooth muscle actin and/or desmin) markers. Nuclear β-catenin and factor XIIIa staining may also be seen in BSNS, but SOX10, epithelial markers, rhabdomyoblastic (myogenin and/or MyoD1), and melanocytic (HMB-45 and/or Melan-A) markers are typically negative [1–4]–except for rare cases with rhabdomyoblastic differentiation that show associated myogenin and/or MyoD1 staining. The vast majority of BSNS harbor *PAX3* gene rearrangements (with *PAX3-MAML3* being the dominant fusion), and PAX3 immunohistochemistry and/or fluorescent in situ hybridization are highly sensitive ancillary tests to support this diagnosis [2, 3, 5–8]. Other fusion partners with *PAX3* include *FOXO1* or *NCOA1*, which are usually associated with rhabdomyoblastic differentiation.

Differential Diagnoses

Neural Tumors

Sinonasal neural tumors – including schwannoma and malignant peripheral nerve sheath tumor (MPNST) – are rare but an important morphologic and immunophenotypic differential diagnosis for BSNS [9, 10]. Although it can rarely surround and entrap benign sinonasal epithelial structures – like BSNS – schwannoma is typically composed of plump spindle cells with fibrillary amphophilic cytoplasm and round to oval nuclei (Fig. 2 and Table 1). Furthermore, while schwannoma usually demonstrates strong and diffuse S100 protein expression, in contrast to biphenotypic sinonasal sarcoma, it also expresses SOX10 and lacks myogenic marker expression [11–14]. Finally, while the morphologic spectrum of MPNST is broad, it is frequently a high-grade tumor, with more conspicuous cytologic atypia and mitotic activity than is usually seen in BSNS [15]. Regardless, given the potential for rhabdomyoblastic differentiation in a small subset of BSNS, particular care should be taken the exclude the possibility of a low-grade MPSNT with rhabdomyoblastic differentiation (so called "Triton tumor"), using immunohistochemistry and/or ancillary molecular tests [16].

Smooth Muscle Tumors

Sinonasal smooth muscle tumors–including leiomyoma and leiomyosarcoma–are also rare but may enter the differential diagnosis for BSNS due to their fascicular appearance and myogenic marker expression [17, 18]. Importantly, in contrast to BSNS, sinonasal smooth muscle tumors typically have a prominent circumscribed or pushing growth pattern (Fig. 3 and Table 1). In addition, the fascicle size is usually larger in sinonasal smooth muscle tumors, and the spindle cells tend to have a more elongated appearance with moderate eosinophilic cytoplasm and oval nuclei. Furthermore, while sinonasal smooth muscle tumors may share myogenic marker expression with BSNS, they will uniformly lack neural marker expression. Finally, as above with MPNST, the

Table 1 Key morphologic features and ancillary test information for top 10 spindled differentials

Diagnosis	Morphologic features	Ancillary tests
Biphenotypic sinonasal sarcoma	Infiltrative fascicles of bland-appearing spindle cells with eosinophilic cytoplasm and tapered nuclei; may entrap epithelial structures and involve bone	Variable co-expression of neural (S100 protein) and myogenic (SMA and/or desmin) markers; subset of tumors with rhabdomyoblastic (myogenin and/or MyoD1) marker and/or TLE-1 expression; lack of SOX10, melanocytic (HMB-45 and/or Melan-A), and epithelial marker expression; PAX3 IHC or FISH is sensitive for detecting *PAX3* rearrangements
Nerve sheath tumors	Schwannoma = plump spindle cells with fibrillary amphophilic cytoplasm and round to oval nuclei; may entrap epithelial structures MPNST = increased nuclear atypia and mitotic activity	Schwannoma = diffuse SOX10 and S100 protein expression; lack of myogenic, rhabdomyoblastic, and melanocytic markers MPNST = patchy or absent S100 staining; increased Ki-67 proliferative index; loss of H3K27me3 staining by IHC; aneuploidy by CMA
Smooth muscle tumors	Leiomyoma = large fascicles of bland-appearing elongated spindle cells with eosinophilic cytoplasm and oval nuclei; circumscribed growth pattern Leiomyosarcoma = increased nuclear atypia and mitotic activity	Leiomyoma = diffuse myogenic marker expression; lack of neural, rhabdomyoblastic, melanocytic, and epithelial markers Leiomyosarcoma = variable myogenic marker expression; increased Ki-67 proliferative index; aneuploidy by CMA
Rhabdomyosarcoma	Mixture of small round blue cells, plump spindle cells with eosinophilic cytoplasm, and/or pleomorphic rhabdoid cells; solid and infiltrative growth patterns	Desmin and rhabdomyoblastic marker expression; variable SMA and epithelial marker expression; lack of neural and melanocytic markers; FISH may show *PAX3* rearrangement and PAX3 IHC may be positive in alveolar type
Glomangiopericytoma	Solid hypercellular sheets of bland-appearing spindle cells with amphophilic cytoplasm and round to oval nuclei; prominent thin-walled vessels with perivascular hyalinization; circumscribed growth pattern	Smooth muscle actin, CD99, and cyclin D1 expression; nuclear and cytoplasmic β-catenin staining (mutant pattern); lack of desmin, CD34, STAT6, neural, rhabdomyoblastic, melanocytic, and epithelial marker expression; *CTNNB1* exon 3 hotspot mutation by Sanger sequencing or NGS
Solitary fibrous tumor	Haphazardly arranged spindle cells with scant amphophilic cytoplasm and round to oval nuclei within fibrous stroma; prominent thin-walled vessels with perivascular hyalinization; may have an infiltrative growth pattern	CD34 and CD99 expression; lack of myogenic, neural, rhabdomyoblastic, melanocytic, and epithelial marker expression; STAT6 IHC is sensitive and specific for detecting *STAT6* rearrangements
Synovial sarcoma	Solid expansile sheets of hypercellular fascicles composed of spindle cells with amphophilic cytoplasm and tapered nuclei; may be biphasic with admixed epithelial component; intermediate to high mitotic activity with variable pleomorphism	CD99 and TLE-1 expression; variable epithelial marker expression (particularly in biphasic cases); lack of myogenic, neural, rhabdomyoblastic, and melanocytic marker expression; SS18-SSX IHC is sensitive and specific for *SS18-SSX1* and *SS18-SSX2* fusions
Teratocarcinosarcoma	Heterogeneous biphasic neoplasm with admixed immature and mature epithelial and mesenchymal components, including frequent primitive neuroepithelial elements	IHC patterns correspond to the morphology of specific epithelial and mesenchymal components; SALL4 expression; SMARCA4 (BRG1) loss by IHC
Spindle cell (sarcomatoid) squamous cell carcinoma	Malignant spindle cell proliferation with varied morphologic and architectural features; may be biphasic with admixed islands of atypical squamous epithelium; typically associated with prior or concurrent intraepithelial squamous dysplasia and/or invasive squamous cell carcinoma	Variable expression of epithelial and squamous markers (p63 and p40) may show myogenic and/or rhabdomyoblastic marker staining in a subset of cases; p53 IHC may show strong and diffuse nuclear staining (mutant pattern); lack of neural and melanocytic marker expression and nuclear β-catenin
Spindle cell melanoma	Infiltrative sheets of tightly packed nests composed of epithelioid to spindled cells with amphophilic cytoplasm, round nuclei, and conspicuous nucleoli; intermediate to high mitotic activity with variable pleomorphism; intratumoral melanin pigment may be present	Diffuse SOX10 expression with variable S100 protein and melanocytic marker staining; lack of epithelial, myogenic, and rhabdomyoblastic marker expression

CMA chromosomal microarray, *FISH* fluorescent in situ hybridization, *IHC* immunohistochemistry, *MPNST* malignant peripheral nerve sheath tumor, *NGS* next-generation sequencing, *SMA* smooth muscle actin

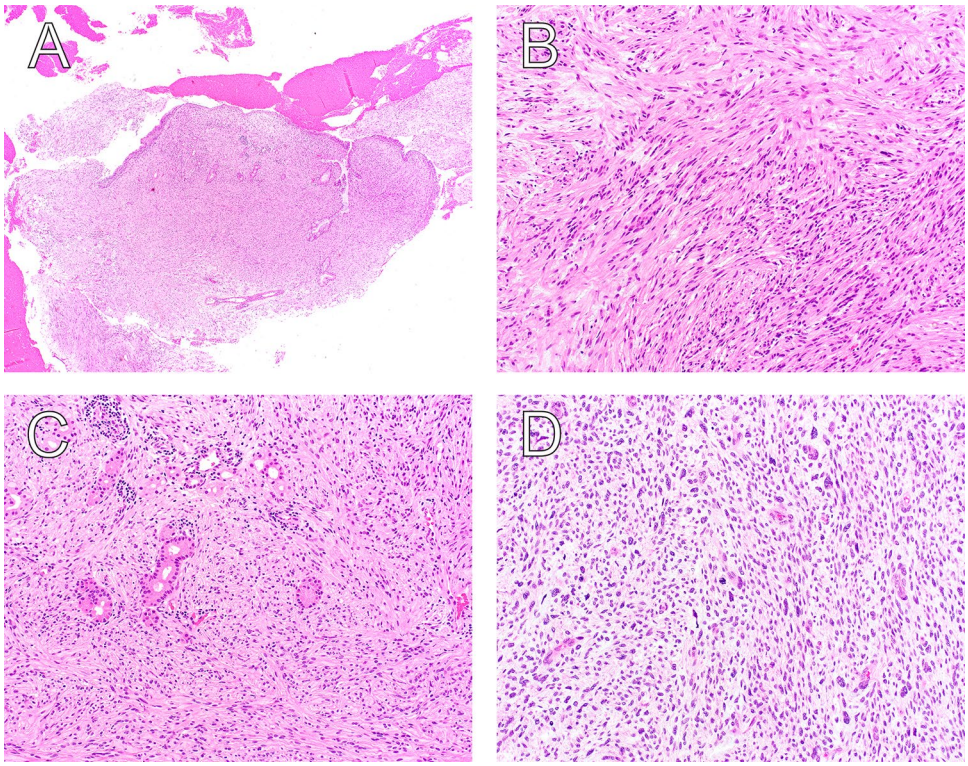

Fig. 2 Nerve sheath tumors. **A**–**C** Benign nerve sheath tumors (i.e., schwannoma) may entrap benign epithelial structures – like BSNS – but have characteristic fibrillary amphophilic cytoplasm and round to oval nuclei and a distinct immunoprofile (see Table 1). In addition, S100 protein expression by benign nerve sheath tumors is an immunophenotypic mimic of BSNS. **D** Malignant peripheral nerve sheath tumors are rare but demonstrate increased nuclear atypia and mitotic activity, as well as unique ancillary test results (see Table 1). [Magnification: A = 4X; and B–D = 20X]

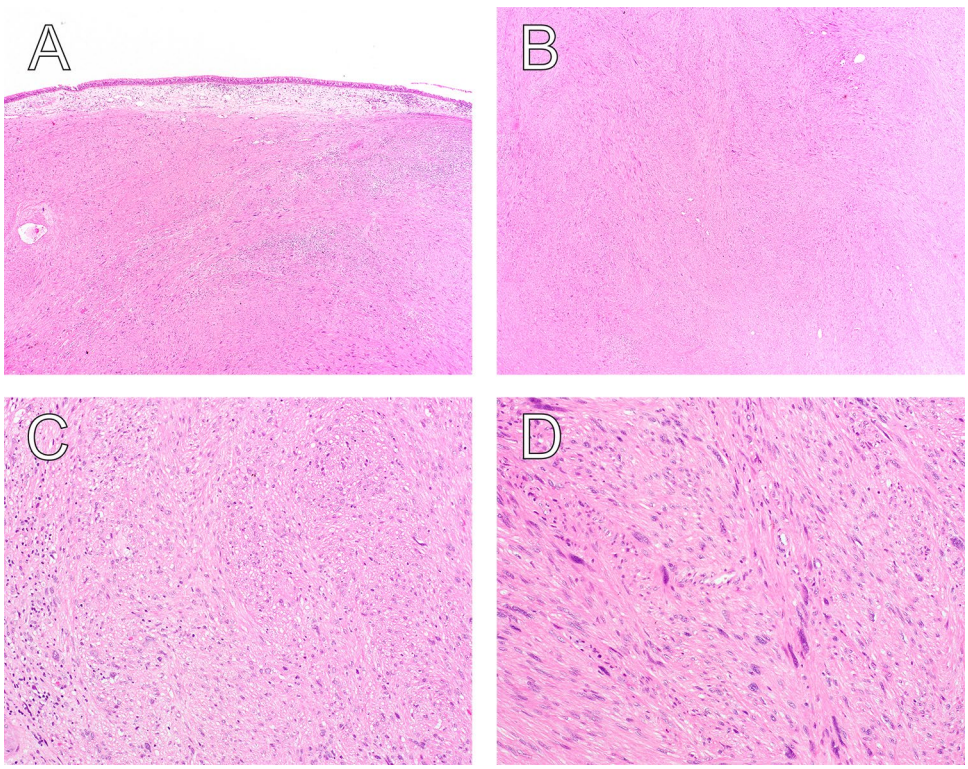

Fig. 3 Smooth muscle tumors. **A**, **B** Low-power views highlight the predominantly circumscribed growth pattern and prominent large fascicular architecture of sinonasal smooth muscle tumors. **C** Benign smooth muscle tumors (i.e., leiomyoma) is comprised of bland-appearing elongated spindle cells with eosinophilic cytoplasm and oval nuclei; **D** malignant smooth muscle tumors (i.e., leiomyosarcoma) show increased nuclear atypia and mitotic activity, as well as unique ancillary test results (see Table 1). Smooth muscle actin expression by smooth muscle tumors is an immunophenotypic mimic of BSNS. [Magnification: A and B = 4X; and C and D = 20X]

degree of cytologic atypia and mitotic activity present in leiomyosarcomas is usually well beyond that of BSNS.

Rhabdomyosarcoma

Rhabdomyosarcoma is the most common primary sarcoma of the sinonasal tract, and its variable expression of smooth muscle actin can confound the diagnosis of other sinonasal sarcomas – including BSNS [10, 19]. Furthermore, the vast majority of sinonasal rhabdomyosarcomas are alveolar type and harbor *PAX3-FOXO1* gene rearrangements and, thus, may represent an immunohistochemical and molecular mimic of BSNS when using PAX3 immunohistochemistry or *PAX3* fluorescent in situ hybridization, respectively [8, 19]. That being said, sinonasal rhabdomyosarcoma typically has a small round blue cell appearance with admixed pleomorphic rhabdoid cells (Fig. 4 and Table 1), and when present, spindle cell areas are focal and composed of plump cells with eosinophilic cytoplasm. The spindle cell/sclerosing variant of rhabdomyosarcoma is rare but may occasionally involve the sinonasal tract in adults; due to its predominant spindled morphology and frequent smooth muscle actin staining, this variant may be challenging to distinguish from BSNS [20]. Importantly, in contrast to BSNS, rhabdomyoblastic marker expression is typically diffuse, and neural marker staining is usually negative; while co-expression of epithelial markers may be seen in rhabdomyosarcoma, they are absent in BSNS [19].

Glomangiopericytoma

Glomangiopericytoma is another uncommon mesenchymal sinonasal tumor that represents a partial immunophenotypic mimic of BSNS [21]. Although originally termed "sinonasal-type hemangiopericytoma," it is now known to be unrelated to "soft tissue hemangiopericytoma" (i.e., solitary fibrous tumor; see below). Instead, as the current preferred name suggests, glomangiopericytoma is presumed to correspond to a unique sinonasal type of perivascular myoid cell tumor – similar to myopericytoma, glomus tumor, etc. Glomangiopericytoma is a hypercellular tumor composed of solid sheets of bland-appearing spindle cells with moderate amphophilic cytoplasm, round to oval nuclei, and prominent thin-walled ("hemangiopericytoma-like") vessels with perivascular hyalinization (Fig. 5 and Table 1). While not significant in BSNS, extravasated erythrocytes and numerous eosinophils and mast cells are common in glomangiopericytoma. Furthermore, in contrast to BSNS, the growth pattern of the glomangiopericytoma is usually circumscribed, and S100 protein is absent. Finally, glomangiopericytomas typically harbor hotspot *CTNNB1* exon 3 mutations and demonstrate nuclear β-catenin staining [22, 23]; as described above, the latter may also be seen in BSNS but is unrelated to a *CTNNB1* mutation.

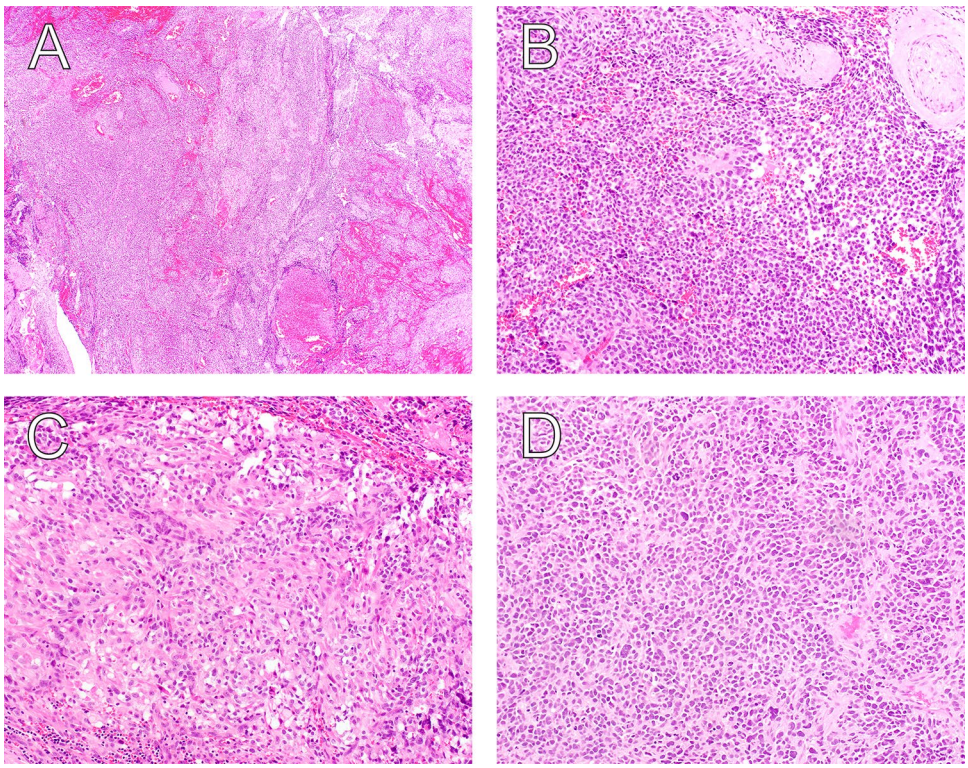

Fig. 4 Rhabdomyosarcoma. **A** Low-power view of rhabdomyosarcoma shows a solid hypercellular tumor composed of a mixture of small round blue cells (**B**), plump spindle cells with eosinophilic cytoplasm (**C**), and/or pleomorphic rhabdoid cells (**D**). Alveolar rhabdomyosarcomas will demonstrate a *PAX3* gene rearrangement by fluorescent in situ hybridization – a molecular mimic of BSNS. [Magnification: A = 4X; and B–D = 20X]

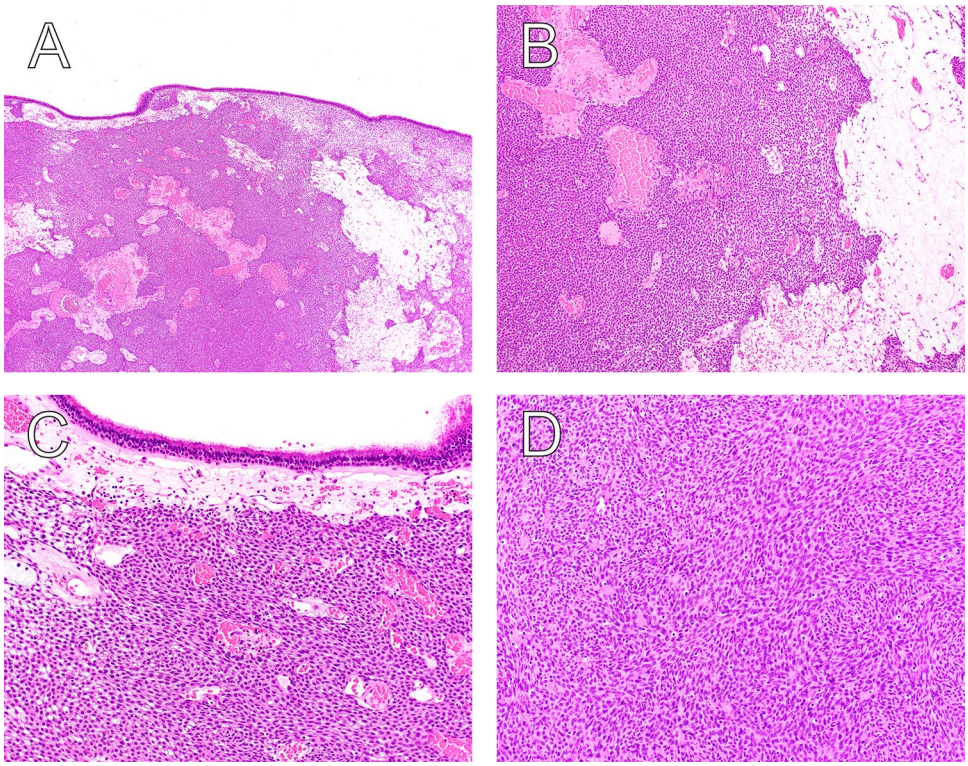

Fig. 5 Glomangiopericytoma. **A**–**D** Low- and high-power views highlight the circumscribed growth pattern of glomangiopericytoma (**A**, **C**), which is composed of solid hypercellular sheets of bland-appearing spindle cells with amphophilic cytoplasm and round to oval nuclei and associated prominent thin-walled vessels with perivascular hyalinization (**B**, **D**). Smooth muscle actin expression by glomangiopericytoma is an immunophenotypic mimic of BSNS. [Magnification: A = 4X; B = 10X; and, C and D = 20X]

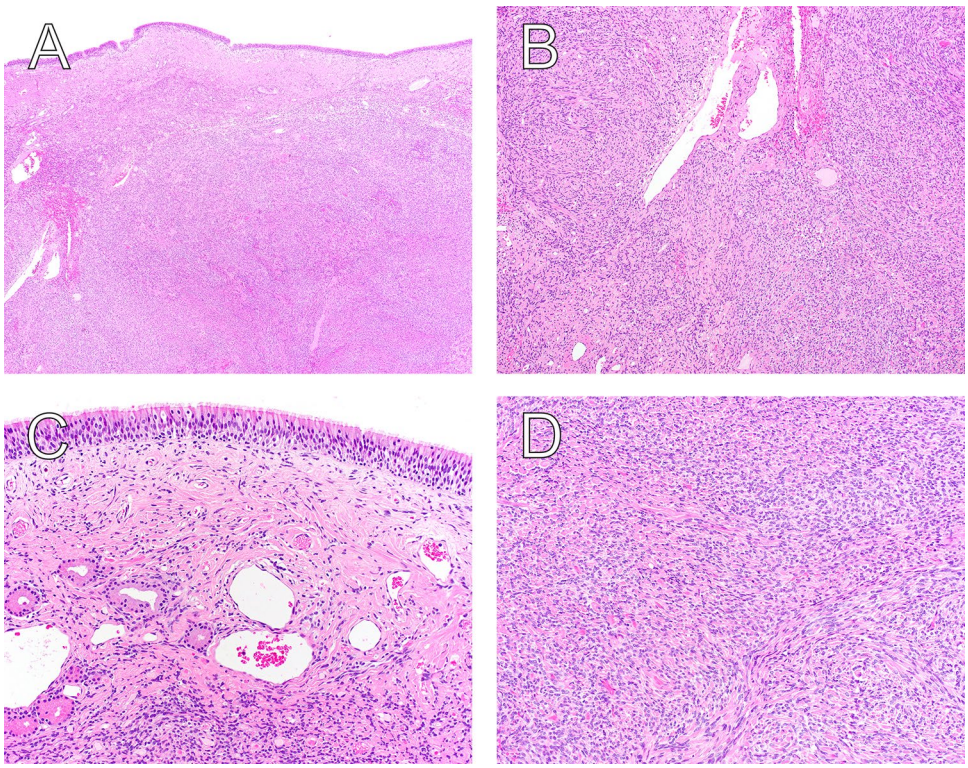

Fig. 6 Solitary fibrous tumor (SFT). **A**–**D** Low- and high-power view of SFT extensively involving sinonasal subepithelial stroma, including peripheral infiltration of benign epithelial structures (**A**, **C**). SFT is composed of haphazardly arranged spindle cells with scant amphophilic cytoplasm and round to oval nuclei within fibrous stroma with prominent admixed thin-walled vessels with perivascular hyalinization (**B**, **D**). SFT is a morphologic mimic of BSNS. [Magnification: A = 4X; B = 10X; and, C and D = 20X]

Solitary Fibrous Tumor

Solitary fibrous tumor (SFT) is an important entity in the different diagnosis for BSNS [24, 25]. It is typically composed of bland-appearing spindle cells with scant amphophilic to eosinophilic cytoplasm and round to oval nuclei, arranged haphazardly within fibrous stroma with prominent hyalinized thin-walled vessels (Fig. 6 and Table 1), and like BSNS, SFT may have an infiltrative growth pattern. However, SFTs are uniformly negative for myogenic and neural marker expression and, instead, show diffuse CD34 and STAT6 expression – the latter a result of pathognomonic *NAB2-STAT6* gene rearrangements present in the vast majority of tumors [26–28].

Synovial Sarcoma

Synovial sarcoma (SS) is a rare soft tissue malignancy of uncertain histogenesis that uncommonly involves the sinonasal tract and is an important entity in the differential diagnosis for BSNS [10, 29]. It is typically composed of monotonous spindle cells with amphophilic cytoplasm and tapered nuclei, arranged in solid expansile sheets of hypercellular fascicles (Fig. 7 and Table 1); however, subsets of synovial sarcomas are biphasic with an admixed glandular epithelial component, which may resemble entrapped benign sinonasal epithelial structures in BSNS. Despite this morphologic overlap, synovial sarcomas are negative for myogenic and neural marker expression in the vast majority of tumors and, instead, show diffuse TLE-1 and SS18-SSX expression on immunohistochemistry–the latter, a result of characteristic *SS18-SSX1* or *SS18-SSX2* gene rearrangements in the vast majority of tumors [30–33]. While patchy to diffuse TLE-1 expression has been reported in BSNS, mitotic activity in synovial sarcoma is usually intermediate to high, and variable pleomorphism may be present [29, 34, 35]. In diagnostically challenging cases, ancillary molecular testing may be helpful.

Teratocarcinosarcoma

Teratocarcinosarcoma is a unique and very rare sinonasal tumor that, due to its often multiphasic appearance, may occasionally enter the differential diagnosis for BSNS [36]. It is a heterogeneous that neoplasm comprised admixed immature and mature epithelial and mesenchymal components, including primitive neuroepithelial elements (Fig. 8 and Table 1). Dependent on sampling, these features may only be seen in isolated foci, making interpretation challenging. Immunohistochemical staining patterns correspond to the morphology of specific epithelial and mesenchymal elements and may include myogenic and/or neural marker staining; however, SALL4 is typically expressed throughout the tumor [37]. In addition, there is frequent bi-allelic

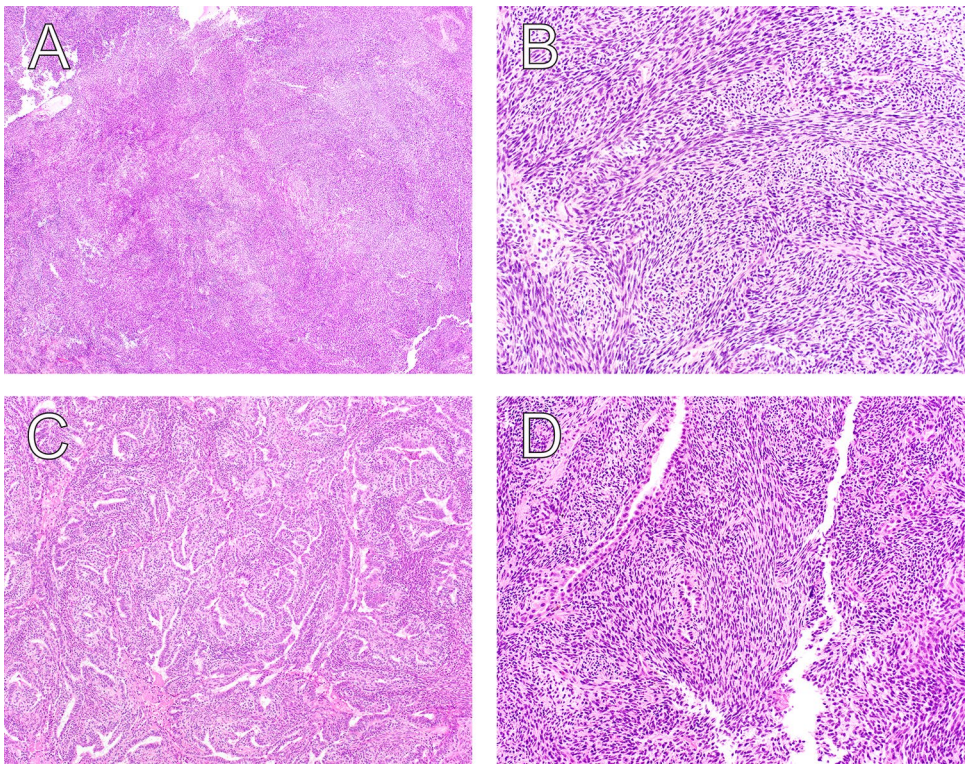

Fig. 7 Synovial sarcoma (SS). **A**, **B** Low- and high-power view of synovial sarcoma shows a solid hypercellular tumor composed of fascicles of spindle cells with amphophilic cytoplasm and tapered nuclei, intermediate to high mitotic activity, and variable pleomorphism. **C**, **D** Subsets of SS are biphasic with admixed epithelial components that can mimic entrapped benign sinonasal epithelial structures and, thus, can be a morphologic mimic of BSNS. [Magnification: A = 4X; C = 10X; and, B and D = 20X]

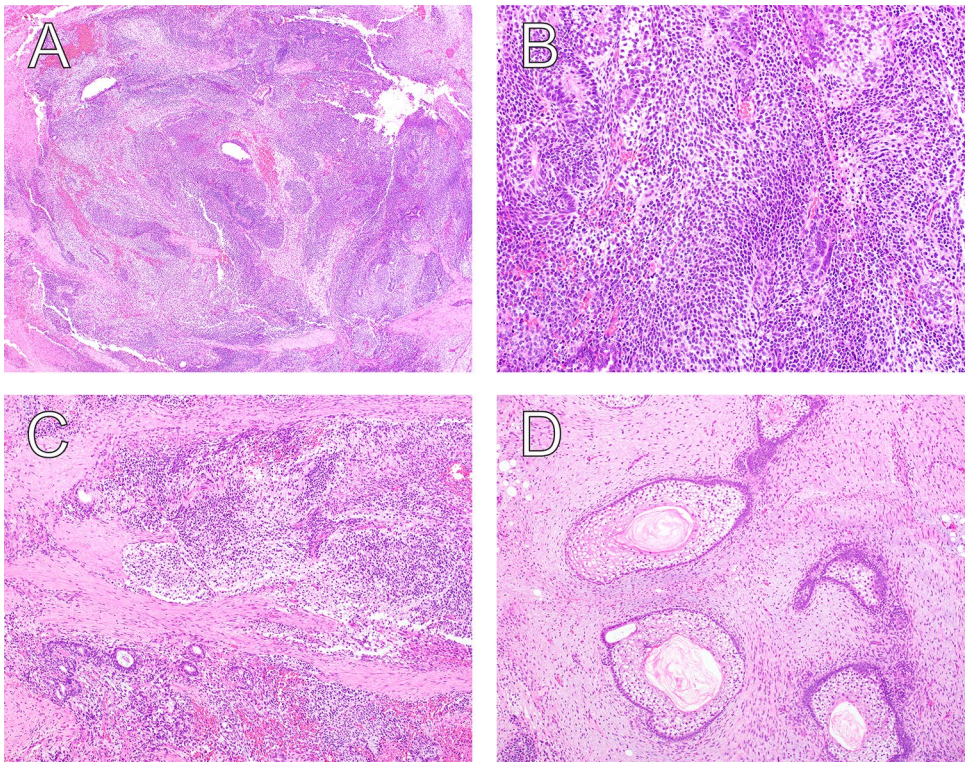

Fig. 8 Teratocarcinosarcoma. **A** Low-power view of teratocarcinosarcoma shows a heterogeneous biphasic neoplasm with admixed epithelial and mesenchymal components, including primitive neuroepithelial elements (**B**–**D**). The presence of these admixed epithelial components can mimic entrapped benign sinonasal epithelial structures, and thus, teratocarcinoma can be a morphologic mimic of BSNS. [Magnification: A = 4X; C and D = 10X; and, B = 20X]

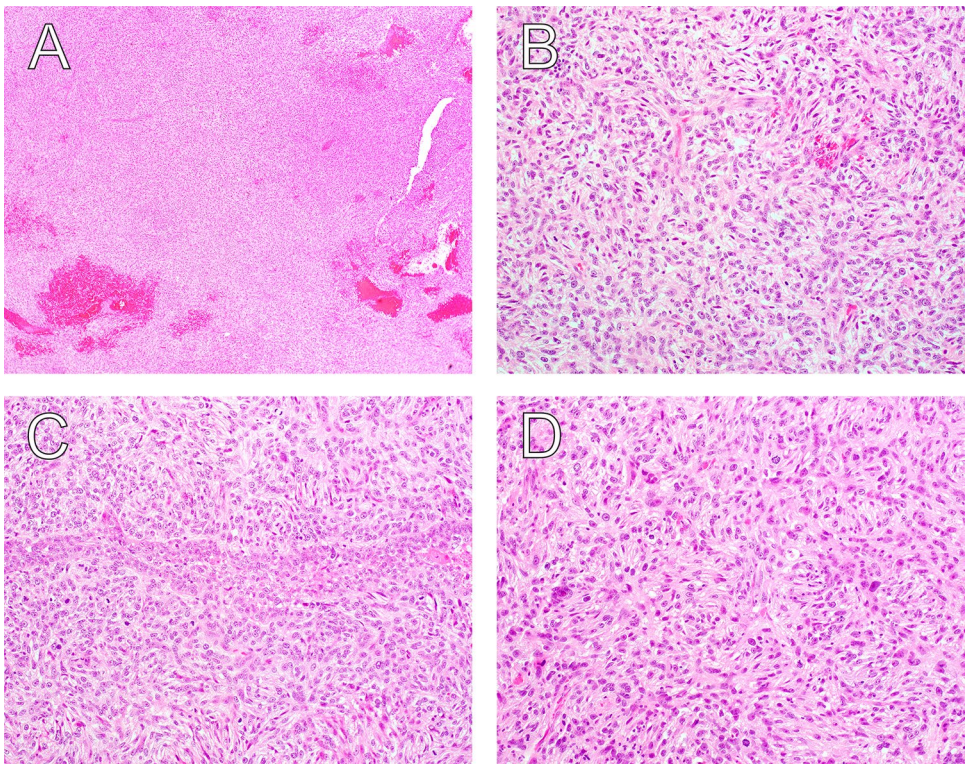

Fig. 9 Spindle cell (sarcomatoid) squamous cell carcinoma (SCC). **A** Low-power view of spindle cell (sarcomatoid) SCC shows a solid hypercellular tumor comprised of monotonous spindle cells with pale to amphophilic cytoplasm, enlarged and irregular vesicular nuclei, and small nucleoli, arranged haphazardly within loose myxoid stroma (**B**). A biphasic appearance with admixed islands of atypical squamous epithelium and areas of conspicuous mitotic activity and pleomorphism are common (**C**, **D**). Because SCC is the most common malignancy of the sinonasal tract, spindle cell (sarcomatoid) SCC is an important differential diagnostic consideration for BSNS. [Magnification: A = 4X; and, B–D = 20X]

inactivation of *SMARCA4* in sinonasal teratocarcinosarcoma with corresponding SMARCA4 (BRG1) loss by immunohistochemistry in most tumors [38].

Spindle Cell (Sarcomatoid) Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is the most common primary sinonasal malignancy and, thus, should always be considered in the differential diagnosis for BSNS [39, 40]. Spindle cell (sarcomatoid) SCC is a subtype of invasive SCC characterized by a malignant spindle cell proliferation with varied morphologic and architectural features (i.e., myogenic, rhabdomyoblastic, etc.) (Fig. 9 and Table 1). In addition, most of these tumors are biphasic with admixed islands of atypical squamous epithelium and are associated with prior or concurrent intraepithelial squamous dysplasia and/or invasive SCC. As such, in contrast to BSNS, spindle cell (sarcomatoid) SCC usually demonstrates at least focal epithelial differentiation, with pan-cytokeratin and squamous (p63, p40, and CK5/6) marker expression, and p53 immunohistochemistry may show strong and diffuse nuclear staining (mutant pattern). Even if the tumor lacks epithelial markers, spindle cell (sarcomatoid) SCC is usually negative for actins and S100 protein staining and lacks nuclear β-catenin expression.

Spindle Cell Melanoma

While less common than SCC, melanoma is another primary sinonasal malignancy that may enter the differential diagnosis for BSNS [41, 42]. Similar to other primary sites, the morphologic spectrum of sinonasal melanoma is broad, but in general, it is composed of epithelioid to spindled cells with amphophilic cytoplasm, round nuclei, and conspicuous nucleoli, arranged in infiltrative sheets of tightly packed nests with intermediate to high mitotic activity, variable pleomorphism, and occasional intratumoral melanin pigment (Fig. 10 and Table 1). Like sinonasal neural tumors, SOX10 and S100 protein are typically expressed in sinonasal melanoma, which also expresses melanocytic markers but is negative for actins and other myogenic markers.

Conclusions

BSNS is a unique spindle cell lesion with a characteristic infiltrative growth pattern that frequently entraps surface epithelium, shows a biphenotypic immunoprofile with variable neural and myogenic marker expression, and harbors pathognomonic *PAX3-MAML3* gene rearrangements in most tumors. While together these features are diagnostic of BSNS, other sinonasal spindle cell lesions may show morphologic, immunophenotypic, and/or molecular overlap. As

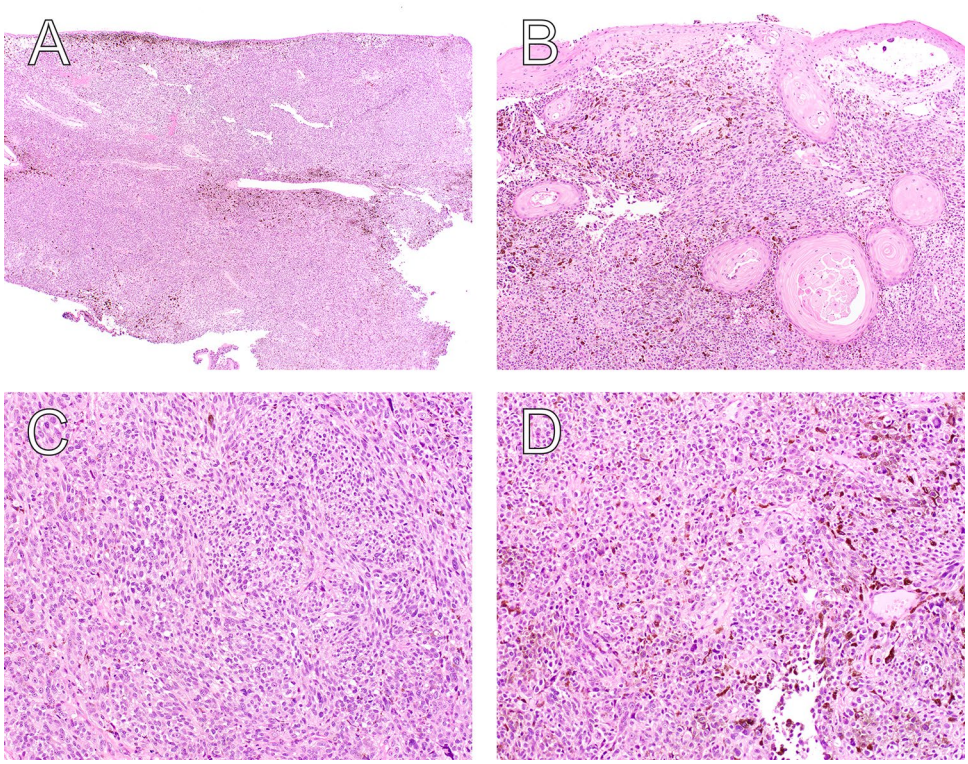

Fig. 10 Spindle cell melanoma. **A**–**D** Low- and high-power view of melanoma shows sinonasal subepithelial stroma extensively involved by a solid hypercellular tumor composed of epithelioid to spindled cells with amphophilic cytoplasm, round nuclei, and conspicuous nucleoli, intermediate to high mitotic activity with variable pleomorphism, and admixed intratumoral melanin pigment. Melanoma is a morphologic and immunophenotypic mimic of BSNS. [Magnification: A = 4X; B = 10X; and, C and D = 20X]

such, it is critical to be aware of the entities in the differential diagnosis for BSNS and have a framework to approach this challenging diagnosis. As always, morphologic evaluation should be central to the work up of sinonasal spindle cell lesions, and particular attention should be paid to cellular morphology, tumor architecture and growth pattern, and the presence of admixed epithelial elements. That being said, immunohistochemistry is also a key part of the diagnostic approach to sinonasal spindle cell lesions, and depending on the list of specific differential diagnoses formulated from the morphologic evaluation, a focused set of immunostains to characterize expression of neural, myogenic, epithelial, rhabdomyoblastic, and/or melanocytic markers should be sufficient to arrive at the final diagnosis in most cases. In the subset of cases for which diagnostic uncertainty persists despite this limited set of immunostains, additional ancillary tests for tumor-specific molecular alterations (i.e., PAX3 immunohistochemistry and/or fluorescent in situ hybridization for BSNS, SS18-SSX immunohistochemistry for synovial sarcoma, etc.) and/or expert head and neck pathology consultation may be helpful for definitive diagnosis.

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Code Availability Not applicable.

Declarations

Conflict of interest The author declares that they have no conflicts of interest or competing interests.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to Participate For this type of study, informed consent is not required.

Consent for Publication For this type of study, consent for publication is not required.

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