HHS Public Access

Author manuscript

Hum Pathol (N Y). Author manuscript; available in PMC 2021 October 15.

Published in final edited form as:

Hum Pathol (N Y). 2021 June ; 24: . doi:10.1016/j.ehpc.2021.200491.

Biphenotypic sinonasal sarcoma: Report of 3 cases with a review of literature

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Abstract

Biphenotypic sinonasal sarcoma (BSNS) is a rare recently described distinct spindle cell sarcoma which arises exclusively in the sinonasal region and is characterized by concomitant neural and myogenic differentiation. Before this neoplasm was characterized, most were classified as other entities including adult fibrosarcoma, monophasic synovial sarcoma and malignant peripheral nerve sheath tumor. By immunohistochemistry, these tumors characteristically express S100 and smooth muscle actin (SMA) and/or muscle specific actin (MSA). Most cases harbor rearrangements of *PAX3* (paired box gene 3), and the most frequent translocation partner is *MAML3* (mastermind like transcriptional coactivator 3). Herein, we described three cases of BSNS involving the nasal cavity with or without paranasal sinus involvement. We also did a literature review of the clinical features, histologic and immunophenotypic findings, cytogenetics, pathogenesis and behavior of this rare entity.

Keywords

Sinonasal sarcoma; Head and neck sarcoma; Spindle cell neoplasm; *PAX3*; *MAML3*

1. Introduction

Malignant spindle cell tumors of the head and neck account for about 1% of all head and neck malignancies and 5–15% of all sarcomas in adults [1]. There are eight major histologic types of head and neck sarcomas in the 2017 *World Health Organization* classification, each of which have many variants. The most common are unclassified/undifferentiated pleomorphic sarcoma, fibrosarcoma, angiosarcoma and malignant peripheral nerve sheath tumor (MPNST) [1]. The histologic classification of

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

these sarcomas has important prognostic significance [2,3]. Rhabdomyosarcoma, MPNST, osteosarcoma and angiosarcoma are the more aggressive histologic types [4–9]. The 5-year survival rate varies from 31% in the most aggressive sarcomas to 80% in the least aggressive subtypes [2,10]. Although surgery is the primary modality of treatment of all these various subtypes, adjuvant radiotherapy or chemotherapy may be administered in more aggressive tumors. Due to the rarity and morphologic overlap between the various subtypes, the histologic diagnosis of sinonasal sarcomas is often challenging, especially on small biopsy material.

In 2012, Lewis et al. [3] described a group of low grade spindle cell sarcomas arising exclusively in the sinonasal tract that show concomitant neural and myogenic differentiation. They noted the histologic resemblance of this group with adult fibrosarcoma, monophasic synovial sarcoma, and MPNST. Interestingly, review of their prior cases resulted in reclassification of 5 of them, 3 were originally interpreted as fibrosarcoma and 2 were thought to be of peripheral nerve sheath origin (schwannoma or MPNST). The authors designated these tumors as low-grade sinonasal sarcoma with neural and myogenic features due to the biphenotypic marker expression by immunohistochemistry. The same group subsequently renamed this entity *biphenotypic sinonasal sarcoma* (BSNS). More recent studies have further characterized the clinical, morphologic and immunophenotypic features as well as genetic aberrations that characterize BSNS. An encounter with three cases of BSNS prompted our review of the literature on this topic.

2. Case 1

2.1. Clinical presentation

A 55-year-old non-smoker Caucasian woman presented with a six-month history of left sided nasal congestion and headaches that had progressed to a point that she could hardly breathe through her left nostril. She had tried saline nasal spray and intranasal steroids with no relief. A month prior to presentation she noticed a mass in the left nasal cavity. She had a prior history of obesity, asthma, multinodular goiter, Barrett's esophagus, fibromyalgia and osteoarthritis. Examination of the nose showed nasal septum deviated to the right and a polypoidal mass obstructing the left nasal cavity with associated edematous turbinates and clear white rhinorrhea. CT sinus showed an enhancing soft tissue lesion involving the left nasal cavity with extension into the maxillary, frontal and ethmoid sinuses, abutting the orbit and base of skull (Fig. 1). The patient underwent endoscopic debridement followed by piecemeal resection of this mass. Beginning seven weeks following resection, the patient underwent radiation therapy to the tumor site (6000 cGy in 30 fractions) over the course of six weeks. Follow-up imaging and clinical examination showed no evidence of disease recurrence over the next 32 months.

2.2. Pathologic features

We received multiple polypoidal fragments of soft tissue which on histologic examination showed an unencapsulated and infiltrative cellular spindle cell neoplasm involving the sinonasal bones (Fig. 2a–2b). The spindle cells were arranged in fasicles (Fig. 2c) and showing uniform nuclei and rare mitotic figures (Fig. 2d). The associated vessels

demonstrated a hemangiopericytomatous growth pattern. There were interspersed benign sinonasal-type glands (Fig. 2e). The stroma was composed of thin strands of collagen with scattered small lymphocytes and hemosiderin laden macrophages. Ulceration, hemorrhage and necrosis were not present. Rare foci showed plump tumor cells with abundant eosinophilic cytoplasm (Fig. 2f).

2.3. Immunohistochemical features

A panel of immunohistochemical studies were performed which demonstrated diffuse S100 and smooth muscle actin (SMA) positivity and focal desmin and cytokeratin 8/18 positivity whereas EMA and CD34 were negative (Fig. 3a–3d). On the basis of these histologic and immunohistochemical findings, the diagnosis of BSNS was rendered.

3. Case 2

3.1. Clinical presentation

A 43-year-old woman with history of rhinoplasty performed 20 years ago presented with a four-month history of right nasal obstruction which became more pronounced after a respiratory infection. CT sinus showed a partially calcified soft tissue mass, 5.1 cm in cranial caudad dimension, within the right aspect of the nasal cavity and protruding within the right maxillary, ethmoid and frontal sinuses as well as the superior aspect of right orbit. Nasal endoscopy showed a large polyp emanating from the right middle meatal region and extending into the right nasal cavity that was surgically removed in its entirety. The patient's postoperative course was without complications, but she was subsequently lost to follow-up.

3.2. Pathologic features

The debridement showed a hypercellular proliferation of monotonous spindle cells arranged in fascicles with a herringbone pattern. The cells were uniform with scant cytoplasm, indistinct borders and elongated hyperchromatic nucleus with fine granular chromatin and low mitotic activity.

3.3. Immunohistochemical features and cytogenetics

The tumor showed immunoreactivity for S100, SMA and focally for desmin but CD34, STAT6, EMA and myogenin were negative. There was no nuclear accumulation of beta-catenin. Fluorescent in situ hybridization (FISH) performed using custom bacterial artificial chromosome (BAC) probes showed rearrangement of *PAX3* and *MAML3* genes.

4. Case 3

4.1. Clinical presentation

A 70-year-old woman initially presented with a chief complaint of memory loss was found to have an incidental 2.2 cm left superior meatus lesion on MRI brain in addition to minimal white matter microvascular ischemic disease. Upon further questioning, the patient revealed that she had also been experiencing rhinorrhea and left sided nasal congestion. The curettings of this lesion were received in the pathology department as a consult.

Postoperatively, the patient did not receive any adjuvant therapy and is doing well with no signs of recurrence for at least 13 months following the resection.

4.2. Pathologic features

The histologic review showed a spindle cell tumor with variable degree of cellularity and fibrotic stromal component. The tumor involved the submucosa and was associated with an overlying hyperplastic glandular epithelium. The lesional cells had scant cytoplasm and bland fusiform nuclei lacking pleomorphism or increased mitotic activity.

4.3. Immunohistochemical features

Submitted immunohistochemical studies showed focal positivity for S100 and SMA, while nuclear beta-catenin, desmin, pan-cytokeratin, p63, HMB45, CD31 and CD34 were negative, and Ki-67 proliferative index was very low (<1%).

5. Discussion and review of literature

We described three cases of *Biphenotypic sinonasal sarcoma* (BSNS) which is a recently described and rare neoplasm. There are close to 100 cases reported in the literature. The available data shows that these tumors tend to be more common in females (male to female ratio of 1:3). However, a study by Peng et al. has shown on a multivariate analysis that adults' head and neck sarcomas tend to be more common in males [2]. The median age of patients is 48 years (range of 24–87 years). Tumors commonly involve the nasal cavity and ethmoid sinus [3,11–19,36]. In some cases, tumor extension into the orbit, skull base involvement, and intracranial extension were identified (Table 1). There are no known etiologic factors and no evidence of association with neurofibromatosis. The presenting symptoms include difficulty breathing, facial pressure, congestion and occasionally facial pain, mild epiphora and diplopia. Some patients have reported to have had history of sinonasal surgery for apparently benign processes such as angiofibroma and benign polyps. On imaging, the tumor appears as a heterogeneously enhancing, destructive lesion with adjacent hyperostotic bone.

5.1. Pathologic features

The tumors have all been surgically excised in piecemeal and the tissue fragments have been described as red-pink to tan or gray, polypoid, and somewhat more firm than typical inflammatory nasal polyps.

5.2. Histologic findings

Key histologic features [3] are (1) an infiltrative, highly cellular, and uniform spindle cell proliferation with a scant matrix; (2) a hemangiopericytomatous vascular pattern; and (3) interspersed, benign sinonasal type glands within the spindle cell proliferation (Fig. 2c–2f). The invasion of sinonasal bones is seen only in about 24% of the cases. The spindle cells are arranged into medium to long fascicles and may show classic herringbone pattern. Increased mitotic activity, hemorrhage, necrosis, and ulceration are not seen. The nuclei are predominantly elongated but maybe focally wavy. The background stroma is composed of delicate collagen strands, scattered small lymphocytes and occasionally hemosiderin-laden

macrophages. The overlying respiratory epithelium may show benign proliferation and entrapment in the form of small glands or cystic spaces with mucinous metaplasia or may mimic an inverted papilloma. Some cases have a few large cells with, eccentric nuclei, prominent nucleoli and cells with bright, fibrillary eosinophilic cytoplasm and focal cross-striations suggestive of rhabdomyoblastic differentiation.

5.3. Immunohistochemical findings

BSNS are characterized by S100 and SMA and/or muscle specific actin (MSA) expression [3,11–17,19–23]. A recently described monoclonal antibody for evaluation of expression of PAX3, a transcription factor that plays a critical role in the formation of tissues and organs during embryonic development, is reported to be highly sensitive (100%) and specific (98%) for BSNS [13,23,36]. The other immunostains that have been reported positive are beta-catenin (nuclear) [12,14,21,22,24], factor XIIIa [12], PAX8 [23], desmin [3,11–14,16,17,19,21,36], cytokeratin AE1/AE3 [3,11,14,36], CD34 [3,11,36] and TLE1 [12]. Additionally, Andreasen et al. [14] reported 3 cases with cytoplasmic positivity for STAT6. SOX-10 [11,12,14,21,36], estrogen receptor (ER) [3], and progesterone receptor (PR) [3] are consistently negative. The cases with rhabdomyoblastic differentiation show nuclear MyoD1 [11,13–16,21] and myogenin expression [11,12,16,17]. In one case reported by Chitguppi et al. [18] and 27 cases reported by Loarer et al. [36], the tumor showed focal MyoD1 in absence of any morphologically apparent rhabdomyoblastic differentiation (Table 2). Lewis et al. [3] reported the electron microscopic findings of two cases of BSNS as “having elongate nuclei with intracellular collagen and a moderate amount of rough endoplasmic reticulum and occasional subplasmalemmal filaments with dense bodies,” a specialized feature that may be seen in myogenic cells among others.

5.4. Cytogenetics and molecular genetics

In 2012, Lewis et al. [3] performed karyotypic analysis of two BSNS that showed t(2;4)(q37.1;q31.3) chromosomal translocation, which had not been reported in any of the neoplasms considered in the differential diagnosis.

The BSNS phenotype is characterized by aberrant expression of genes involved in neuroectodermal and myogenic differentiation, which closely simulates the developmental roles of *PAX3* [13]. During development, *PAX3* plays important roles in the differentiation and migration of neural-crest derived cells [13]. Specifically, *PAX3* functions at a nodal point in melanocytic, neuronal and skeletal muscle differentiation programs, promoting lineage commitment and blocking terminal differentiation. *MAML3*, on the other hand, is a member of the mastermind-like (MAML) family of transcriptional coactivators for the Notch signaling pathway involved in a variety of pivotal cell processes. Wang et al. [13] generated *PAX3-MAML3* cDNA from BSNS tumor mRNA and subcloned into a mammalian expression vector and using transient transcription assays showed that *PAX3-MAML3* consistently activates *PAX3*-driven receptor plasmids by 40-fold or more, whereas wild-type *PAX3* activated these receptors approximately 8-fold.

It seems that the *PAX3-MAML3* fusions are important in the pathogenesis of BSNS through deregulation of lineage commitment coupled with activation of Notch signaling programs promoting neoplastic growth. More recent studies have also shown similar results [4,6,8,18].

Novel cases have been identified showing *PAX3-NCOA1* and *PAX3-FOXO1* fusions that are also seen in alveolar rhabdomyosarcomas (ARMS) [4,6,16,17]. (Table 3) Interestingly, tumors reported to have *PAX3-NCOA1* fusion [11] show morphologic and immunophenotypic features with focal rhabdomyoblastic differentiation. Even though BSNS and ARMS share the same chromosomal translocations, unlike BSNS, ARMS show nests and sheets of primitive rounded cells that are diffusely positive for desmin and MSA separated by variably prominent fibrous septa. In addition, the gene expression profiles of BSNS show higher levels of neurogenic and cytokine-related genes, metalloproteinase genes, and *MYOCD* (myocardin), in contrast to ARMS that show high levels of skeletal myogenesis related-genes [13].

More recently, Loarer et al. [36] reported 2 cases with *PAX3-WWTR1* fusion and 1 case with *PAX3-NCOA2* fusion.

5.5. Differential diagnosis

BSNS is a challenging diagnosis because of its rarity and the need to be differentiated from a large spectrum of head and neck spindle cell neoplasms with neurogenic, myogenic, fibroblastic, and vascular lineages (Table 4), and from benign reactive proliferations.

Schwannomas may show uniform interlacing fascicles of spindle cells like BSNS, but they classically have alternating hypocellular and hypercellular areas, nuclear palisading, and perivascular hyalinization, which are features that are not described in BSNS. Although schwannomas are diffusely positive for S100, they also show diffuse expression of SOX10 and lack expression of PAX3, SMA, desmin and beta-catenin [23,25–27].

Malignant triton tumor, a type of MPNST with rhabdomyoblastic differentiation commonly associated with neurofibromatosis 1, may show expression of muscle markers in addition to focal S100. But triton tumor is a high-grade tumor that presents as a rapidly enlarging mass and histologically shows nuclear pleomorphism, hyperchromasia, brisk mitotic activity and geographic areas of necrosis, unlike BSNS. Polycomb Repressive Complex 2 (PRC2) inactivating mutations can be detected by Histone 3 lysine 27 trimethylation (H3K27me3) loss. In addition, triton tumors are negative for PAX3 and positive for SOX10 which excludes BSNS. Low-grade forms that represent only a minority of MPNSTs on the other hand pose a greater challenge and subsets of BSNS were probably previously classified as low-grade MPNST/triton tumors. However, alternating dark and light cellular areas, association with peripheral nerves and only focal positivity for S100 [26] in these tumors are useful in making the distinction with BSNS.

Monophasic synovial sarcomas may show similar histologic and immunohistochemical features as BSNS but it is important to note that synovial sarcomas are extremely rare in the sinonasal tract with only 12 reported cases in the literature to date [28]. Even though TLE1 positivity may lead to confusion, these tumors are characterized by EMA positivity

and a diagnostic t(X;18)(p11;q11) translocation, resulting in *SS18-SSX* rearrangements not identified in BSNS.

Glomangiopericytoma (GPC), like BSNS, is composed of highly cellular proliferation of uniform cells with open vascular pattern. A distinctive feature of GPCs is presence of short fascicles and whorls, perivascular accentuation and grenz zone under the respiratory epithelium and, further, the nuclei in GPCs tend to be round and ovoid rather than elongated as in BSNS. Even though GPCs are almost always positive for SMA and express nuclear beta-catenin, they almost always lack S100 expression and are consistently negative for desmin [29]. Another key point of distinction is that beta-catenin is much more diffuse in GPC than BSNS, in which it tends to be focal.

Solitary fibrous tumors (SFTs) may show a similar uniform spindle cell proliferation and hemangiopericytoma-like vascular pattern but can be distinguished from BSNS by presence of ropey bundles of collagen rather than delicate collagen strands that are seen in BSNS. Moreover, SFTs are positive for CD34 and also characteristically for STAT6 (nuclear), both of which would be negative in BSNS. They also lack positivity for S100, SMA and desmin [30].

Leiomyosarcomas can also have similar histologic appearance, but the spindle cells in leiomyosarcoma have cigar-shaped nuclei with perinuclear halos, in contrast to BSNS. While both entities express smooth muscle markers, leiomyosarcomas are negative for S100 and beta-catenin [31,32].

Adult fibrosarcomas show a herringbone pattern with long fascicles of spindle cells and can be very similar to BSNS, although the fascicles are longer and the collagen deposition is more developed and coarser in the former. Moreover, they lack concurrent expression of SMA and/or desmin, S100, and nuclear beta-catenin and should be considered only as diagnosis of exclusion [33]. Fibromatosis is another morphologically similar neoplasm that shows broad fascicles of bland spindle cells with myofibroblastic appearance in a more collagenized background and with cellularity much less than BSNS. Although it shows nuclear beta-catenin and may show focal expression of SMA and/or desmin, it lacks positivity for S100 [27,34].

Finally, inverted papilloma and respiratory epithelial adenomatoidhamartoma may enter the differential diagnosis especially on biopsies because of the prominent surface epithelial proliferation seen in association with BSNS, yet these entities lack an associated spindle cell proliferation.

A panel of immunohistochemical stains that includes S100, SMA and/or MSA, MyoD1, beta-catenin and PAX3 may be helpful in recognizing BSNS, especially on small biopsies.

5.6. Treatment and prognosis

Clinically, BSNS behaves in a relatively indolent manner compared to other head and neck sarcomas [35]. All the cases so far have been treated either with surgery alone or with combination of radiotherapy. Clinical follow-up has ranged from less than 1 year to 28 years (mean, 8.3 years), however; the details of the methods of surveillance used have not been

provided. Local recurrences have been reported in overall 35% of cases, with no known regional or distant metastases, and two reported cases of tumor related death [12,15]. (Table 1)

6. Conclusions

We described three cases of BSNS which is an uncommon low-grade spindle cell neoplasm in the sinonasal region characterized by concomitant neural and myogenic differentiation. These tumors tend to be more common in females, occur at a median age of 48 years, commonly involve the nasal cavity and ethmoid sinus, and are commonly associated with local recurrence. BSNS is an important entity for pathologists to be familiar with because of the broad differential for head and neck spindle cell tumors and the indolent clinical behavior that distinguishes BSNS from common head and neck sarcomas. Histologically, it can be mistaken for other benign and malignant spindle cell neoplasms but is distinguished by its unique histologic features, expression of S100, SMA and/or MSA and characteristic *PAX3-MAML3* fusion or *PAX3* locus rearrangement seen in majority of the tumors. It is important for pathologists to be aware of this entity to avoid misdiagnosis as a more aggressive process.

7. Patient consent

Written, informed consent for publication of their case was not obtained from the patients.

Acknowledgments

Funding disclosure

All authors confirm that this work is original and has not been published elsewhere nor is it currently under consideration for publication elsewhere.

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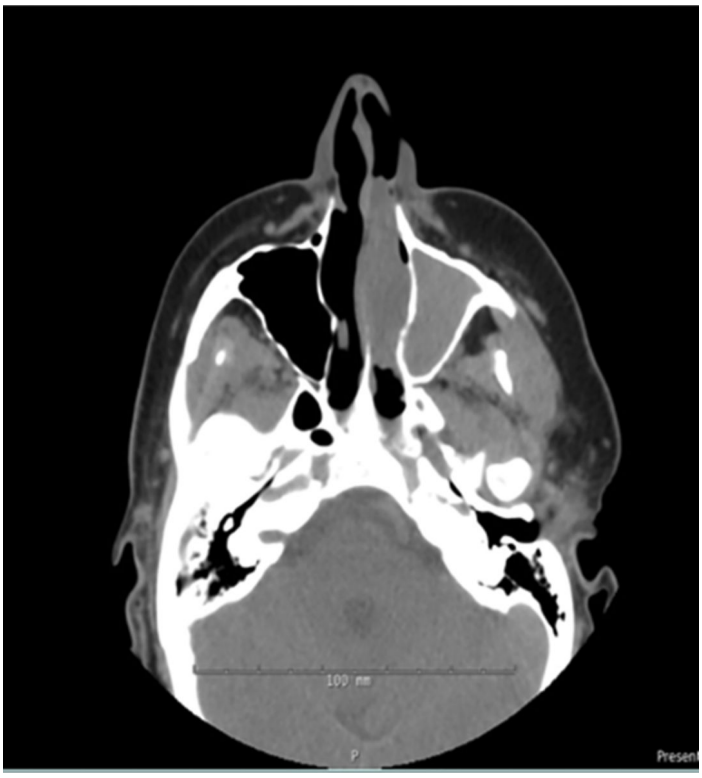

Fig. 1.

Axial CT image showing an enhancing soft tissue lesion involving the left nasal cavity with extension into the maxillary, frontal and ethmoid sinuses, abutting the orbit and base of skull.

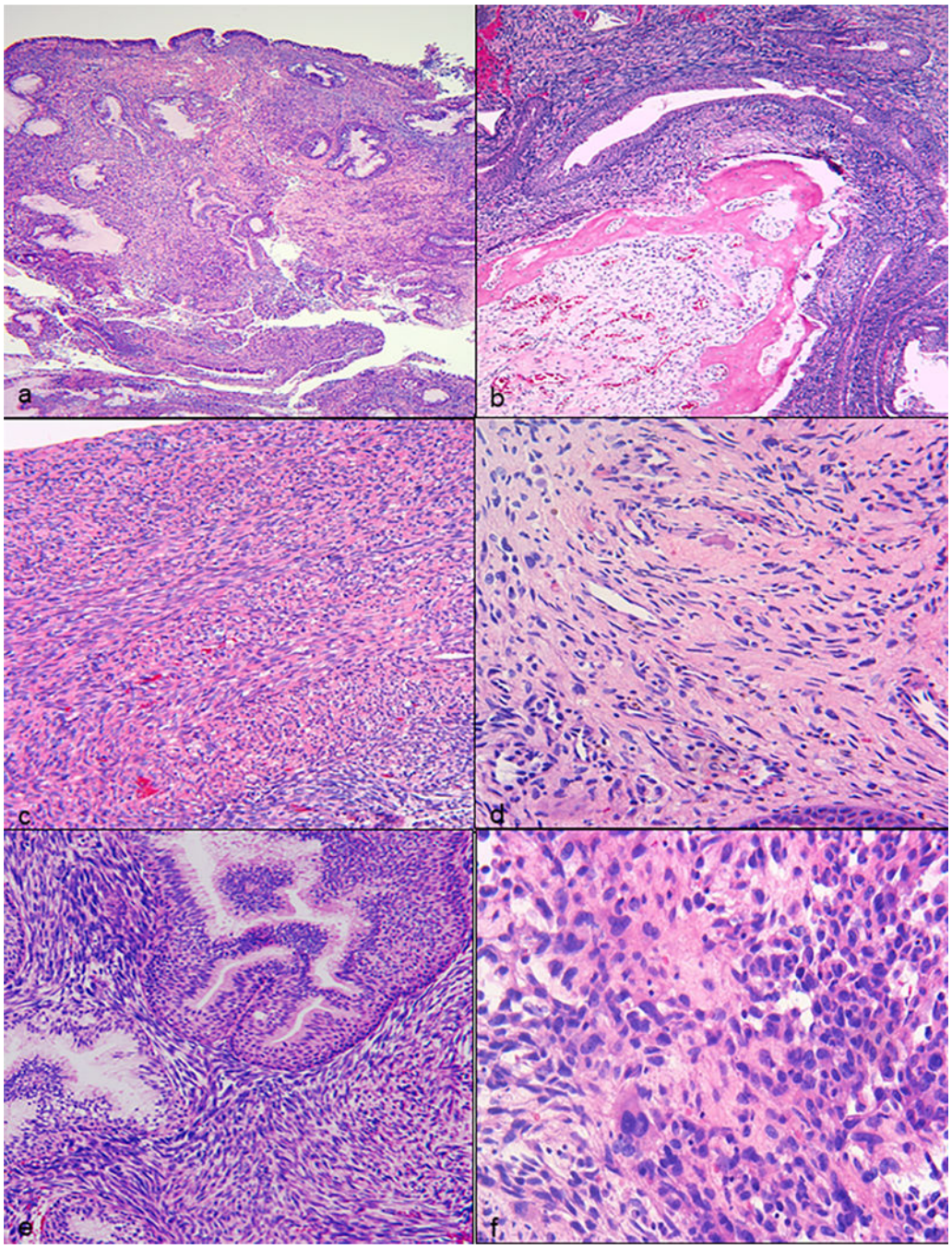

Fig. 2.

Low-power magnification shows a submucosal cellular spindle cell proliferation (Fig. 2a, hematoxylin-eosin, original magnification ×10) that invades the underlying sinonasal bone (Fig. 2b, hematoxylin-eosin, original magnification ×20). The spindle cells are arranged in fascicles with herringbone pattern (Fig. 2c, hematoxylin-eosin, original magnification ×20). Some areas may show spindle cells with wavy nuclei in a background of sparse intercellular collagen, admixed small lymphocytes and hemosiderin laden-macrophages (Fig. 2d, hematoxylin-eosin, original magnification ×40). There is associated benign

glandular proliferation lined by respiratory-type epithelium (Fig. 2e, hematoxylin-eosin, original magnification ×20). Some cases can have rare large plump cells with abundant eosinophilic cytoplasm (Fig. 2f, hematoxylin-eosin, original magnification ×40).

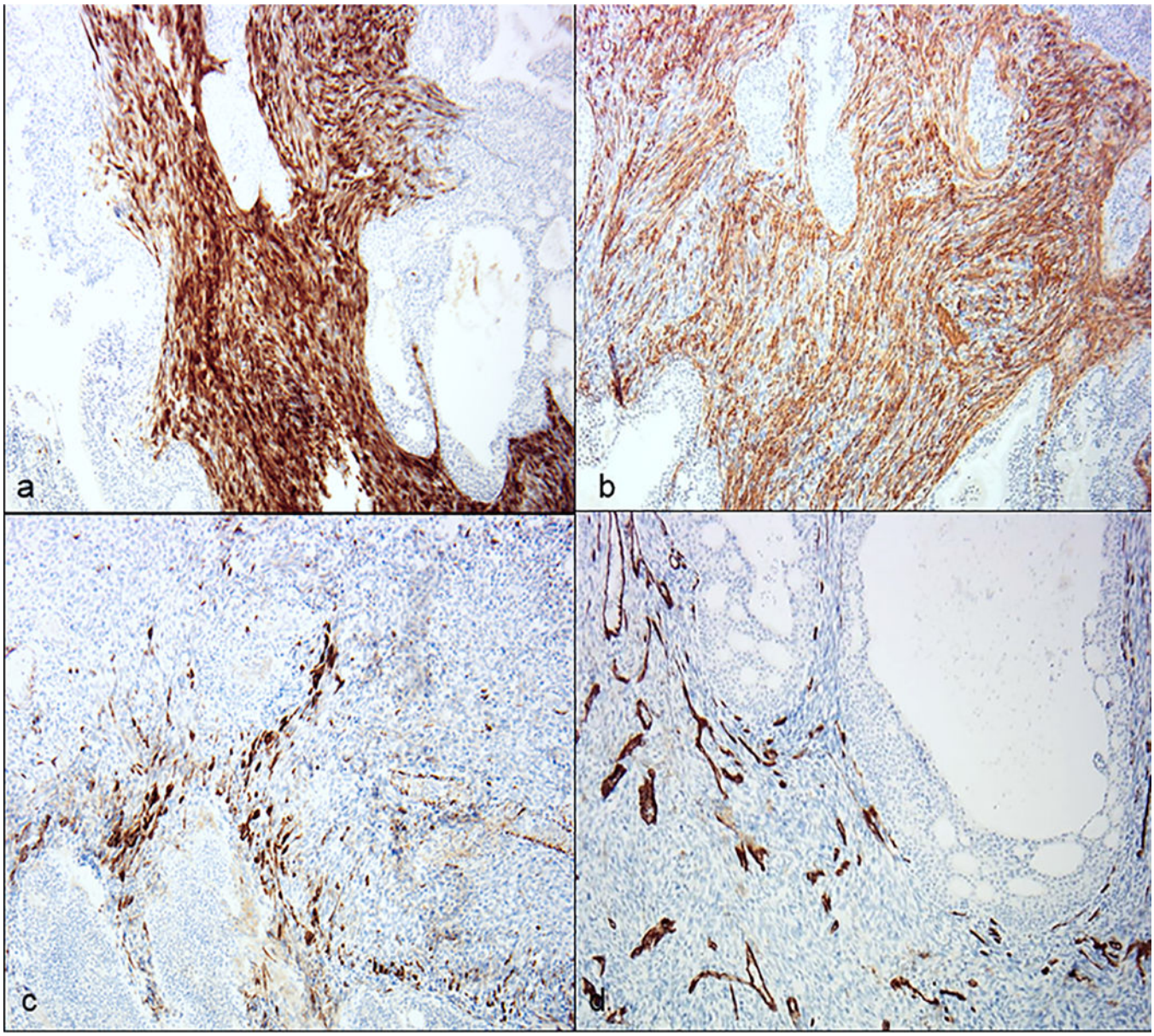

Fig. 3.

The characteristic diffuse positivity for S100 (Fig. 3a) and SMA (Fig. 3b) is seen in the spindle cells of BSNS. Scattered spindle cells show positivity for desmin in case 1 (Fig. 3c). CD34 immunostain is negative in the spindle cells but highlights the endothelial cells of the background vessels (Fig. 3d).

Table 1

Clinicopathological data on reported cases.

	Male to female ratio	Age (years)	Location, no.	Extension into orbit, no.	Skull base involvement, no.	Intracranial Extension, no.	Local recurrence, no.	Tumor related death, no.	Mean Follow Up Time (years)
Our cases	3F	43–70 (median, 55)	Nasal cavity 3/3, ethmoid sinus 2/3, frontal sinus 2/3, maxillary sinus 2/3	1/3	1/3	0/3	0/2	0/2	1.5
Lewis et al. [3] and Wang et al. [13]	1:3	24–85 (median, 48)	Nasal cavity 15/28 and ethmoid sinus 16/28	7/28	3/28	1/28	7/16	0	8.3
Huang et al. [11]	1:1	37–70 (median, 47)	Frontal and ethmoid sinus 3/7, Nasal cavity 2/7 and nasal cavity and ethmoid sinus 2/7	0	0	0	1/4	0	5.6
Cannon et al. [19]	1:3	62–79 (median, 67)	Nasal cavity 2/3, ethmoid sinus 3/3, frontal sinus 3/3	3/3	3/3	3/3	1/2	0	7.8
Rooper et al. [12]	1:3	33–87 (median, 44)	Ethmoid sinus 4/11, Frontal sinus 3/11, Nasal cavity 3/11, Nasal cavity and ethmoid sinus 1/11	2/11	0	1/11	2/7	1/7	6.9
Andreasen et al. [14]	1:2	49–71 (median, 59)	Nasal cavity/ethmoid sinus	0	0	0	1/3	0	5.6
Lin et al. [15]	1F	67	Nasal cavity/maxillary/ethmoid/ frontal/sphenoid sinuses	0	1/1	1/1	0	1/1	N/A (perioperative death)
Fritchie et al. [16]	1:2	31–85 (median, 47)	Nasal cavity/left oropharynx/ ethmoid/frontal sinuses	-	1/9	-	1/3	0	10
Wong et al. [17]	1 M	33	Nasal cavity/sphenoid sinus	0	0	0	0	0	0.4
Chitguppi et al. [18]	1 M	53	Nasal cavity/ethmoid/frontal sinuses	1/1	0	0	0	0	Not provided
Loarer at al [36]	1:3	25–84 (median, 49)	Nasal cavity/ethmoid/frontal sinuses	3/41	4/41	0	8/25	0	5.2

Table 2

Immunohistochemical profile of the reported cases.

	Our cases	Lewis et al. [3]	Powers et al. [22]	Huang et al. [11]	Fritchie et al. [16]	Cannon et al. [19]	Rooper et al. [12]	Jo et al. [23]	Kakkar et al. [24]	Wong et al. [17]	Andreasen et al. [14]	Lin et al. [15]	Wang et al. [13]	Zhao et al. [21]	Triki et al. [20]	Chitguppi et al. [18]	Loarer et al. [36]
SI00, no.	3/3	28/28	1/1	7/7	42/43	3/3	11/11	15/15	-	1/1	3/3	1/1	25/25	3/3	1/1	1/1	41/41
SMA, no.	3/3	23/25	0/1	5/5	39/42	3/3	11/11	14/15	-	1/1	3/3	1/1	22/24	3/3	1/1	0/1	35/39
Nudear beta-catenin, no.	0/3	-	1/1	-	-	-	10/11	-	5/6	-	3/3	-	-	1/3	-	-	6/22
Factor XIII, no.	-	-	-	-	-	-	8/10	-	-	-	-	-	-	-	-	-	-
Desmin, no.	2/3	4/20	-	4/7	16/46	2/3	4/11	-	-	1/1	2/3	1/1 (focal)	4/23	1/3	-	0/1	27/41
Myogenin, no.	0/1	0	0/1	1/7	2/23		3/10			1/1		1/1 (isolated cells)	0/22				8/41
SOX-IO, no.	-	-	-	0/7	-	-	0/11	-	-	-	0/3	-	-	0/3	-	-	0/34
CD34, no.	0/3	5/22	0/1	1/5	-	0	-	-	-	-	0/3	0/1	-	0/3	-	0/1	4/40
MyoDl, no.	-	-	-	3/7	11/43	-	-	-	-	-	1/3	1/1 (focal)	4/22	1/1	-	1/1	32/35
AE1/AE3 or CAM 5.2, no.	1/2	2/21	0/1	2/5	-	-	-	-	-	-	1/3	-	-	0/3	-	0/1	4/38
PAX3 + PAX8, no.	-	-	-	-	-	-	-	15/15	-	-	1/3	-	23/23	-	-	-	29/29
STAT6, no.	0/2	-	-	-	-	-	-	-	-	-	3/3	-	-	-	-	-	-
TLE1, no.	-	-	-	-	-	-	-	-	-	-	3/3	-	-	-	-	-	-

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Table 3

Genetic alterations in reported cases.

	PAX3-MAML3, no.	PAX3-NCOA1, no.	PAX3-FOXO1, no.	PAX3-X, no.	MAML3-X, no.	Other, no.
Our cases	1/1	-	-	-	-	-
Lewis et al. [3]	2/2	-	-	-	-	-
Wang et al. [13]	19/25	-	-	5/25	1/25	-
Huang et al. [11]	4/7	2/7	-	1/7	-	-
Fritchie et al. [16]	24/44	1/44	3/44	11/44	1/44	4/44
Rooper et al. [12]	5/8	1/8	-	2/8	-	-
Wong et al. [17]	-	-	1/1	-	-	-
Lin et al. [15]	-	-	-	1/1	-	-
Andreasen et al. [14]	3/3	-	-	-	-	-
Chitguppi et al. [18]	1/1	-	-	-	-	-
Loarer et al. [36]	37/41	-	1/41	3/41 * –	-	-

* PAX3-WWTR1, 2; PAX3-NCOA2, 1

Table 4

Differential diagnosis of BSNS.

Diagnosis	Histology	Immunohistochemistry	Genetics
Schwannoma	Cellular (Antoni A) and microcystic or loosely packed (Antoni B) areas, vessels with perivascular hyalinization	S100 (+), SMA (−), beta-catenin (−), PAX3 (−)	-
Malignant Triton tumor	Nuclear pleomorphism and hyperchromasia, brisk mitotic activity, necrosis	H3K27me3 (−), S100 (+, focal), Myogenin (+), beta-catenin (−), PAX3 (−)	*SUZ12* or *EED* mutation, *NF1* mutation
Synovial sarcoma	Dense cellular sheets of uniform spindle-shaped dark blue cells	EMA (+), TLE-1 (+)	*SS18-SSX1/2/4*
Glomangiopericytoma	Short fascicles and whorls, perivascular accentuation, grenz zone	SMA (+), beta-catenin (−), S100 (−), desmin (−)	*CTNNB1* mutations
Solitary fibrous tumor	Patternless growth pattern, variably cellular, ropey collagen bundles	CD34 (+), STAT6 (+), SMA (−), S100 (−)	*NAB2-STAT6* fusion
Leiomyosarcoma	Elongated spindle cells with blunt-ended nuclei, perinuclear halos	SMA (+), desmin (+), beta-catenin (−), S100 (−)	-
Fibrosarcoma	Herringbone pattern, usually dense keloid-like collagen	SMA (−/+, focal), desmin (−), S100 (−), beta-catenin (−)	-