



A Rare Sinonasal Malignancy: Biphenotypic Sinonasal Sarcoma

Case Report

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Abstract

Biphenotypic sinonasal sarcoma (BSNS), which has been described in the recent years, is a low-grade spindle cell sinonasal sarcoma characterized by rare neural and myogenic features. It has a slow growth pattern; does not metastasize, but local recurrences are common after surgery. Non-specificity of examination findings and symptoms and similarities of its histopathological features with other spindle cell sarcomas, neural tumors, and skeletal muscle-derived tumors involving the nasal cavity make the diagnosis difficult. Therefore, histopathological features should be evaluated together with immunophenotyping and molecular studies for differential diagnosis. There are very few BSNS cases or case series in the literature. In this report, we reported our clinical approach to a case with BSNS in the right nasal cavity and the histopathological features of the disease in the light of the current literature.

Keywords: Biphenotypic sinonasal sarcoma, paranasal sinus, sarcoma, spindle cell tumor, case report

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Introduction

Biphenotypic sinonasal sarcoma (BSNS) is a rare type of locally aggressive sarcoma that originates from the sinonasal region and is characterized by the molecular rearrangements of the *PAX3* gene. As summarized in Stelow et al. (1), the condition was first described by Lewis et al. in 2012 as “low-grade sinonasal sarcoma with neural and myogenic differentiation. In 2017, the condition was included in the updated World

Health Organization classification of head and neck tumors.

BSNS can arise from any site in the sinonasal tract; however, it typically involves multiple subregions and often originates from the ethmoid sinuses. It may also spread extra sinonasal sites such as orbit and the skull base via the cribriform plate (2).

Patients usually present with non-specific symptoms related to the mass effect of the

tumor, such as nasal obstruction, nasal congestion, recurrent sinusitis attacks, epistaxis, facial pain, and pressure sensation. Ophthalmologic symptoms such as diplopia, proptosis, and blurred vision can also be observed in patients with orbital spread (2, 3).

Histologically, it is defined as a type of spindle cell neoplasia consisting of uniform, elongated nucleated cells, and showing an infiltrative growth pattern. It is characterized by staining of both nervous and muscular system markers in immunohistochemical examinations. Its immunohistochemical profile reveals S100 and actin expression. The diagnosis is further supported by immunopositivity for B-catenin and immunonegativity for SOX10. Fluorescent *in situ* hybridization (FISH) studies reveal numerous rearrangements in the *PAX3* gene, which is a transcription factor involved in the differentiation of neural and myogenic cells (4).

Histological features of BSNS show varying degrees of overlap with tumors such as fibrosarcoma, monophasic synovial sarcoma, peripheral nerve sheath tumors, glomangiopericytoma, and solitary fibrous tumors. This overlap makes it difficult to diagnose (5).

In this case report, we present our clinical approach in a patient with BSNS. We discuss the clinical, histopathological, immunohistochemical, molecular features of the disease and its differential diagnosis in the light of the current literature.

Case Presentation

A 55-year-old female patient was admitted with complaints of right-sided nasal congestion and a feeling of pressure in the right half of the face for about two years. There was no complaint of epistaxis, rhinorrhea, or anosmia. The patient's anamnesis revealed that she had type 2 diabetes mellitus. There was no history of neurofibromatosis in her family.

Nasal endoscopy revealed a pink-colored, hemorrhagic polypoid mass protruding from the right middle meatus to the choana (Figure 1). Other head and neck examinations revealed no abnormalities. Paranasal sinus computed tomography (CT) showed a massive lesion filling the right middle meatus and the right posterior ethmoid cells, and mucosal thickening in the sphenoid sinus (Figure 2). Contrast-enhanced magnetic resonance imaging (MRI) was planned because of the atypical hemorrhagic appearance of the lesion. A mass lesion with an irregular contour of approximately 4x4x1 cm, hyperintense on T2-weighted sequences, hypointense on T1-weighted sequences, enhancing after intravenous contrast agent, and not diffusion restriction, was observed as a result of MRI (Figures 3a and 3b). There was no orbital or skull base extension of tumor. First, an endoscopic biopsy was planned from the mass in outpatient clinic conditions. After the histopathology results

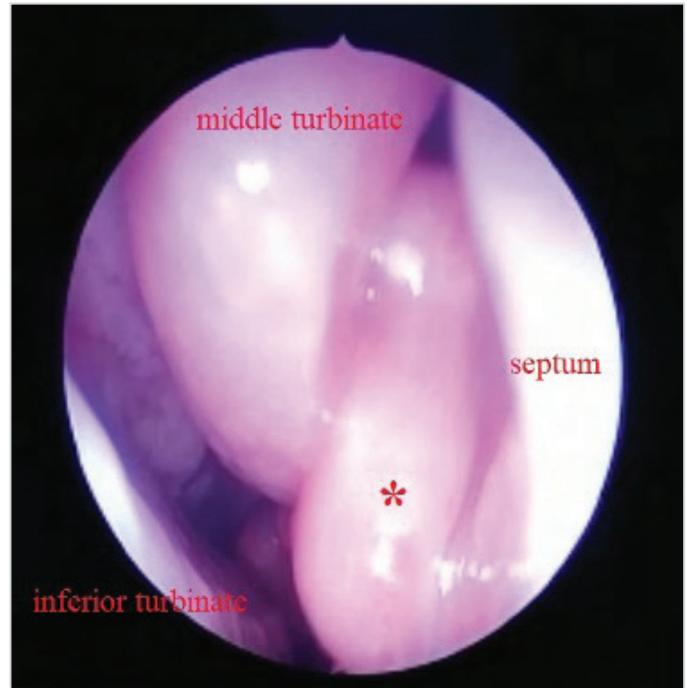


Figure 1. Endoscopic examination revealed a pink-colored hemorrhagic polypoid lesion hanging from the right nasal cavity from the middle meatus

of the biopsies taken twice in a row were reported as nasal polyp, mass resection was planned with transnasal endoscopic sinus surgery in the operating room. During surgery, the mass originating from the sphenoid sinus ostium and posterior ethmoid cells and filling the upper and middle meatus was totally excised. There was no invasion of surrounding tissues. Frozen pathology was studied during the surgery, but a specific diagnosis could not be made. In the final pathology report, this tumor, consisting of infiltrative proliferating spindle cells arranged in fascicles, with low mitotic activity, and without necrosis and atypia, was evaluated as BSNS (Figure 4). The tumor was focal immunopositive for S100 and SMA (smooth muscle antigen). In addition, beta-catenin cytoplasmic and nuclear positive staining and SOX10 negative staining were the other features supporting the diagnosis.

The patient had no complications in the postoperative period. Adjuvant chemotherapy or radiotherapy was not given as there was no extrasinonasal involvement, and the mass was excised with a negative surgical margin. The patient was informed, and the decision was made together with her. Follow up was planned. No recurrence was observed in the 1-year follow-up of the patient.

Discussion

BSNS is a rare tumor characterized by the combination of neural and myogenic histological features. It is more common in females and usually occurs in the fifth decade

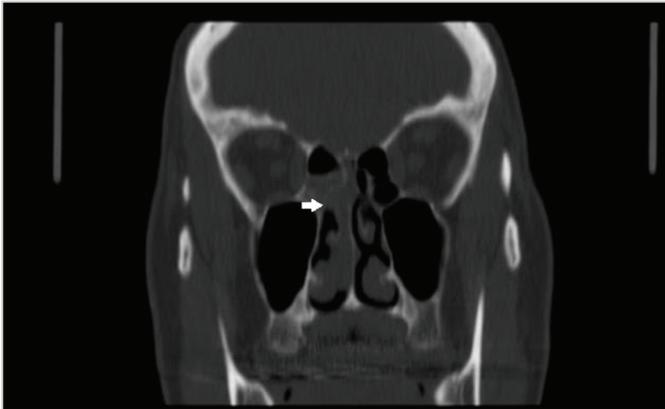


Figure 2. A polypoid mass in the right nasal cavity and mucosal thickening in the sphenoid sinus were observed in the coronal section of paranasal sinus CT
CT: Computed tomography

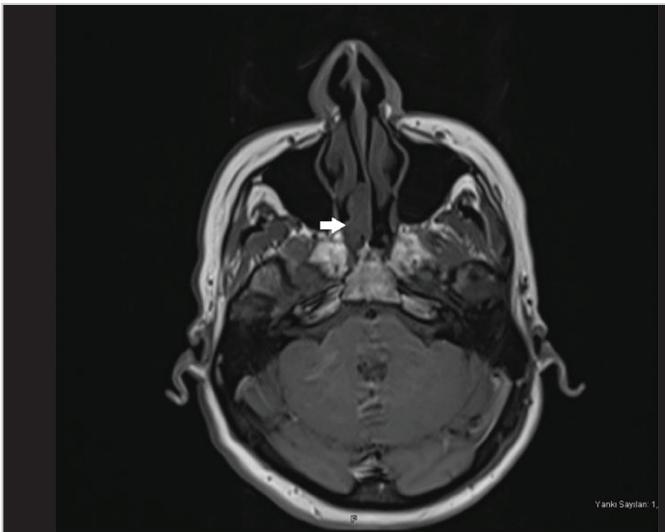


Figure 3.a. A hypointense lesion was observed in the right nasal cavity on T1-weighted sequences of MRI
MRI: Magnetic resonance imaging



Figure 3.b. A hyperintense lesion was observed in the right nasal cavity on T2-weighted sequences of MRI
MRI: Magnetic resonance imaging

(6). The disease progresses slowly and does not metastasize; however, local recurrences occur in approximately one third of the patients within the first five years after surgery (5). The recurrence rate is approximately 40% to 50%, with recurrence-free intervals ranging from less than one year to more than nine years (7). In the literature, mortality from BSNS is quite rare, with only two reported cases of tumor related death (8, 9).

BSNS typically involves multiple subsites, often from the superior nasal cavity and ethmoid sinuses; less frequently, it may originate from the frontal, maxillary, or sphenoid sinuses (6). Extranasal spread may occur with extension into the orbit in 25% of the cases (requiring orbital exenteration) and through the cribriform plate in 10% of cases (7).

Radiological studies are used to support the diagnosis. Radiological findings are variable and not specific for BSNS. On MRI, T1-weighted images are non-specific, on T2-weighted images the mass appears isointense with cerebral gray matter and is more hypointense than many other sinonasal tumors. This feature is seen in fibrotic and hypercellular tumors and is not specific for BSNS. Bone erosion can be observed on CT, and hyperostosis is frequently detected in areas with erosion (80%) (4, 7).

In our case, the patient’s age and sex, the location of the mass in the superior nasal cavity (which originated from the posterior ethmoid cells in front of the sphenoid sinus ostium) was consistent with the general demographic and

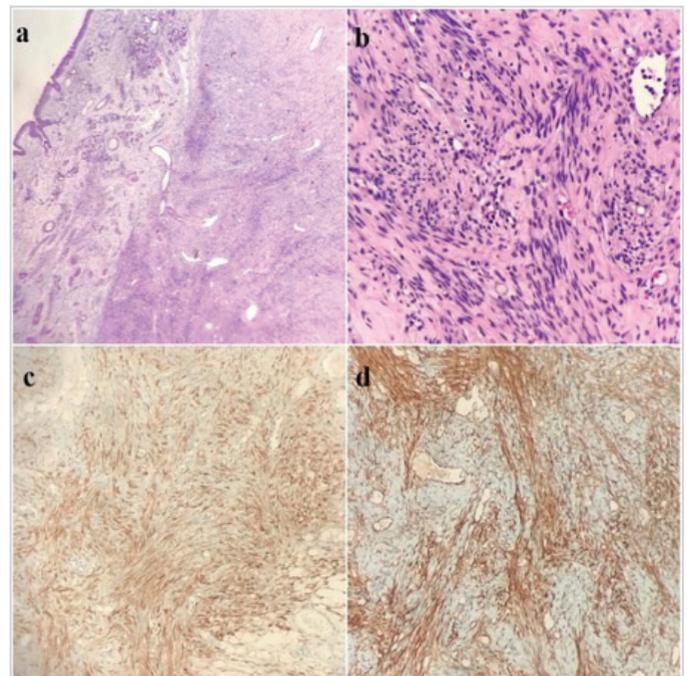


Figure 4. Biphenotypic sinonasal sarcoma a-b) Hematoxylin-eosin staining showing spindle cells arranged in fascicles or in a “herringbone” pattern, and infiltrative proliferation. c) S100 immunopositive staining. d) B-catenin immunopositive staining

typical localization characteristics of BSNS. There was no extrasinonasal (orbital, cribriform plate, and skull base) spread. No bone erosion or hyperostosis was observed on CT. In MRI, it was hyperintense on T2-weighted sequences. These findings supported that CT and MRI were not specific for diagnosis. The key histological features of BSNS are that it is infiltrative, showing an insufficient matrix arranged in fascicles or “herringbone”, a hemangiopericytoma-like vascular pattern and a highly cellular uniformity of spindle cell proliferation with benign sinonasal-type glands interspersed with spindle cell proliferation (10). The nuclei are uniform, pale, and thin. It shows hypercellular features, but mitotic figures are rare. Necrosis and atypia are not observed. Foci of invagination of the respiratory epithelium are common and this may mimic inverted papilloma (1).

The “biphenotypic” characteristic of the tumor comes from the presence of both neural and myogenic markers in immunophenotypic studies. The tumor shows immunoreactivity for both S100 (neural marker) and smooth muscle markers [smooth muscle actin (SMA), muscle specific actin (MSA) or calponin], but the intensity and the extent of staining are variable and may be diffuse or patchy. Other myogenic markers such as desmin, myoD1 and myogenin show patchy or focal staining. Nuclear B-catenin is 90% positive. In particular, SOX10 is consistently negative. In addition, H3K27me3 stains at least partially; TLE1, cytokeratin, CD34, epithelial membrane antigen (EMA) are other markers that show focal positivity (6, 7).

Rearrangements in the *PAX3* gene, which is known to be a transcription factor that plays a critical role in neural and skeletal muscle differentiation, are responsible for the dual differentiation pattern (1). *NTRK3* and *pan-TRK* gene expressions were also shown in most of the cases (11).

In molecular analyses, Fluorescent *in situ* hybridization (FISH) studies, the *PAX3-MAML3* fusion is present in 79%–96% of the cases and pathognomonic for BSNS. It should also be noted that there are reports of patient groups in which *PAX3* gene fusion was not detected (2, 5). This gene rearrangement can distinguish BSNS from its morphologic mimics with a high sensitivity of 100% (8). The *PAX3* gene expression could not be evaluated in our case as FISH cannot be performed in our hospital.

Peripheral nerve sheath tumors, tumors with skeletal muscle and myoid differentiation, solitary fibrous tumors and synovial sarcoma should be included in the differential diagnosis of BSNS (6). These tumors consist of spindle cells that occupy the nasal cavity and show histopathologically mostly fascicular arrangement. This similarity and the wide variety of parameters for diagnosis and the focal or patchy positivity of these parameters make the diagnosis difficult. A definitive diagnosis cannot be made with frozen biopsies.

Schwannoma and malignant peripheral nerve sheath tumors show varying degrees of S100 positivity, as in BSNS. The well-circumscribed growth pattern in schwannomas is an important distinguishing feature (5, 7). In addition, detection of Verocay bodies, Antoni A and B areas, and SOX10 positivity in schwannoma are helpful. Contrary to BSNS, malignant peripheral nerve sheath tumors (MPNST) are distinguished by their high mitotic activity, cellular atypia, and necrosis, as well as SOX10 positive staining. Neurofibromatosis Type 1 is accompanied by 50% of MPNST. Detection of precursor neurofibroma lesions on physical examination supports the diagnosis. In the differential diagnosis of spindle cell rhabdomyosarcomas, it is important to have S100 negativity, higher mitotic activity, more widespread desmin positivity, and diffuse myoD1 positivity in patients with MYOD1 mutation (2, 7). Sinonasal hemangiopericytomas are histologically composed of eosinophilic cells with paler cytoplasm compared to BSNS. The CTNNB1 mutation is held responsible for tumorigenesis and is characterized by nuclear β -Catenin staining with the negativity of S100 and myogenic markers (5, 7). Solitary fibrous tumors may be located in the sinonasal cavity. The difference from BSNS is that it does not show a fascicular or herringbone cellular arrangement and is characterized by the detection of NAB2-STAT6 fusion (2).

Synovial sarcoma can also show TLE1 expression like BSNS. Presence of SS18 fusions in synovial sarcomas is important in differential diagnosis (5).

The main features that distinguish BSNS from other sinonasal malignancies are summarized in Table 1.

The treatment approach is the surgical excision of the lesion. In a review published by Kominsky et al. (3) in 2021, recurrence rates were found comparable between patients who underwent surgical excision only and patients who received radiotherapy after surgical excision. Therefore, the benefit of radiotherapy can be said to be controversial. The rarity of the disease and the small number of cases described in the literature limit the assessment of treatment efficacy and more data is needed. Postoperative radiotherapy and chemotherapy options should be decided by discussing the risks and possible outcomes with the patient (3).

Conclusion

BSNS is a rare tumor characterized by the combination of the histological features of the neural system and the muscular system. It has a slow and silent course and does not metastasize; however, it can progress with recurrences after surgery.

Symptoms, examination findings, and imaging modalities are not specific to BSNS. Detailed evaluation is required for differential diagnosis with spindle cell neoplasms with

Table 1. Summary of the histopathological features distinguishing BSNS from other sinonasal malignancies

	Histopathology		Immunohistochemistry			Molecular features	Other differential features
	Growth pattern	Cytology	S100	SOX10	Myogenic markers (desmin, myogenin)		
Biphenotypic Sinonasal Sarcoma (BSNS)	Infiltrative	Spindle cells arranged in fascicles or in a “herringbone” pattern Low mitosis rate, No necrosis and atypia	+ (patchy or diffuse)	-	Focal +	<i>PAX3</i> gene fusion	B-Catenin + (%90) TLE-1 (focal +) Cytokeratin (focal +) CD34(focal +) EMA(focal +)
Schwannom	Circumscribed but unencapsulated	Verocay body Antoni A ve B areas	+ (diffuse)	+	-		
Malignant peripheral nerve sheath tumor (MPNST)	Fusiform	High mitosis rate Necrosis and atypia +	focal + or -	focal + or -	focal + or -	Loss of Histone H3K27 trimethylation (It is seen in 70% of high grade MPNST)	Neurofibromatosis type 1 accompanies 50% of the cases. Detection of the precursor neurofibroma lesion is important in the diagnosis.
MPNST with rhabdomyoblastic differentiation (Triton tumour)	Fusiform	High mitosis rate Necrosis and atypia +	focal + or -	focal + or -	focal +		
Spindle cell rhabdomyosarcoma	Circumscribed	High mitosis rate	-	-	Focal +	MYOD1 mutation	CTNNB1 mutation
Sinonasal hemangiopericytoma	Polypoid and lobulated	Spinde cells with pale eosinophilic cytoplasm Perivascular hyalinization	-	-	-	CTNNB1 mutation	B-Catenin + (CTNNB1 mutation)
Solitary fibrous tumor	Circumscribed	There is no pattern of fascicles.	-	-	-	NAB2-STAT6 fusion	Diffuse or strong CD 34 staining STAT6 immunopositive (typical)
Synovial sarcoma	Circumscribed		focal + or -	focal + or -	-	SS18-SSX fusion	TLE-1, Cytokeratin, EMA

-: Negative, +: Positive, TLE-1: Transducin-like enhancer of split-1, EMA: Epithelial membrane antigen

oncogenic fusions such as peripheral nerve sheath tumors, tumors with skeletal muscle and myoid differentiation, solitary fibrous tumor, and synovial sarcoma. Histopathological findings, immunohistochemical and molecular studies should be evaluated together.

Main Points

- BSNS should be kept in mind in the differential diagnosis of unilateral nasal masses, especially of those with slow growth patterns.
- It is a diagnostic challenge due to its histologic similarities to other sinonasal malignancies.
- Histology, immunohistochemistry, and molecular studies should be evaluated together.
- Surgical excision is recommended for treatment. Radiotherapy and chemotherapy options are controversial.
- Close follow-up is important because it frequently shows local recurrences.

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