Case Report

Biphenotypic sinonasal sarcoma: An infrequent neoplasm with classical clinical presentation and mimetic histology. Report of two cases

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Abstract

Biphenotypic sinonasal sarcoma (BSNS) is a rare low-grade sarcoma that occurs mainly in the upper sinonasal tract of middle-aged women. It exhibits a dual immunophenotype characterized by the expression of neural and myogenic markers. It is characterized by *PAX3* rearrangement with various fusion partners, being *MAML3* the most frequent. BSNS is a locally aggressive neoplasm, with frequent local recurrences but no metastasis reported. Here, we present the clinical, histological, immunohistochemical, and molecular findings of two new cases of BSNS that fulfill the canonical demographic, clinical, morphologic, and molecular criteria described for this infrequent entity.

Keywords: Biphenotypic, PAX3-MAML3, sarcoma, sinonasal

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INTRODUCTION

Biphenotypic sinonasal sarcoma (BSNS) is a rare, molecularly characterized mesenchymal neoplasm with < one hundred and fifty cases molecularly confirmed in the English literature. It shows dual neural and myogenic immunophenotype and occurs in the sinonasal tract of middle-aged female patients. It shares histological and immunohistochemical characteristics with other mesenchymal neoplasms in the sinonasal tract and harbors pathognomonic *PAX3* rearrangements. To ensure correct diagnosis, it is important to recognize its specific clinical setting of occurrence and determine its classical histologic pattern and immunohistochemical profile.

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CASE REPORT

The cases were retrieved from the institutions to which authors are affiliated.

Immunohistochemical was performed with antibodies against CKAE1/AE3, EMA, C34, S100, SMA, B-catenin, CD99, and Bcl2. Diagnosis was molecularly confirmed by next-generation sequencing.

Case #1

A fifty-six-year-old female who presented with difficulty breathing and nasal congestion. The biopsy yielded multiple fragments of soft, white-grey tissue measuring 2.4 cm in

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aggregate. The patient underwent septostomy and left sphenoidotomy and had no evidence of recurrence after 6 months.

Case #2

A sixty-five-year-old woman who presented with nasal obstruction, hyposmia, hyaline rhinorrhea, and epistaxis. Magnetic resonance imaging (MRI) revealed a 5.8 cm tumor located in the right nasal fossa and ipsilateral sphenoid sinus. The biopsy yielded multiple fragments of grayish tissue measuring 2.5 cm in aggregate. The patient underwent surgery and had no evidence of recurrence after 3 months.

RESULTS

Histology

Both cases revealed infiltrative, highly cellular proliferation of monomorphic, and mildly atypical spindle cells arranged in fascicules. The neoplastic cells had palely eosinophilic cytoplasm with indistinct borders and overlapping, elongated blunted nuclei. Vessels were thin-walled and staghorn-shaped. The entrapped respiratory epithelium was conspicuous.

Mitotic activity and spontaneous tumor necrosis were absent.

Immunohistochemistry and molecular workup

In both cases, the neoplastic cells were patchy positive for SMA, S-100, desmin, BCL2, and nuclear *B*-catenin and negative for CKAE1/AE3, EMA, CK7, CD34, and CD99 [Figure 1].

Both cases were confirmed to harbor *PAX3-MAML3* translocations [Figure 2].

DISCUSSION

BSNS was described in 2012 as a low-grade sinonasal sarcoma with neural and myogenic features[1] and subsequently renamed BSNS.[2] BSNS occurs in the upper sinonasal tract, predominantly in female patients in the fifth and sixth decades.

Approximately 130 cases with molecular confirmation have been reported in the literature, although cohorts overlap makes it difficult to render an exact number.[2,3,4]

BSNS presents with sinonasal symptoms and more commonly occurs in the upper nasal cavities and the ethmoid sinuses and can infiltrate regional bones.

Treatment consists of complete surgical resection, although negative margins are not always achieved, and local recurrences are frequent. Distant metastasis has not been reported.

BSNS are infiltrative and highly cellular. They are comprised monomorphic, mildly atypical spindle cells containing overlapping, elongated, and blunt-ended nuclei with finely granular chromatin. Tumor cells have scant cytoplasm with poorly defined cell borders and are arranged in fascicles. Brisk mitotic activity and tumor necrosis are lacking. The extracellular matrix is inconspicuous, and a hemangiopericytomatous vascular pattern is frequently encountered.

Commonly, the respiratory epithelium is trapped within the neoplasm.

BSNS shows dual neural and myogenic immunophenotype, showing positivity for S100 (100% sensitivity), and SMA (96% sensitivity).[1] Other positive markers include nuclear *B*-catenin (91%)[5-7] and Factor XIII (80%).[6]

Focal cytokeratin staining has been occasionally reported,[1,8] as well as variable expression of desmin and myogenin.[9] BSNS are consistently negative for SOX10.[2,6,9]

Although sensitive, the above-mentioned markers lack individual specificity in the context of tumors that can mimic BSNS. The use of them as part of a panel is then recommended.

PAX3 rearrangements are the consistent genetic alteration in nearly all BSNS, the great majority (76%) being characterized by a t (2;4) (q35.1; q31.3),[2,4] which results in a *PAX3-MAML3* fusion. Approximately 20% of cases harbor rearranged *PAX3* with alternative molecular partners such as *PAX3-FOXO1*[4,5] and *PAX3-NCOA1* fusion.[4,10]

The principal considerations in the differential diagnosis of BSNS include monophasic spindle cell synovial sarcoma (SS), low-grade malignant peripheral nerve sheath tumor, spindle cell rhabdomyosarcoma, and spindle cell melanoma.

Monophasic SS can be distinguished on morphological grounds from BSNS by the significantly higher mitotic count, the presence of interstitial "ropey" collagen fibers, and areas of calcification in the former.

SS and BSNS can exhibit overlapping immunohistochemical features, with subsets of SS expressing S100 and SMA and subsets of BSNS exhibiting focal positivity for epithelial

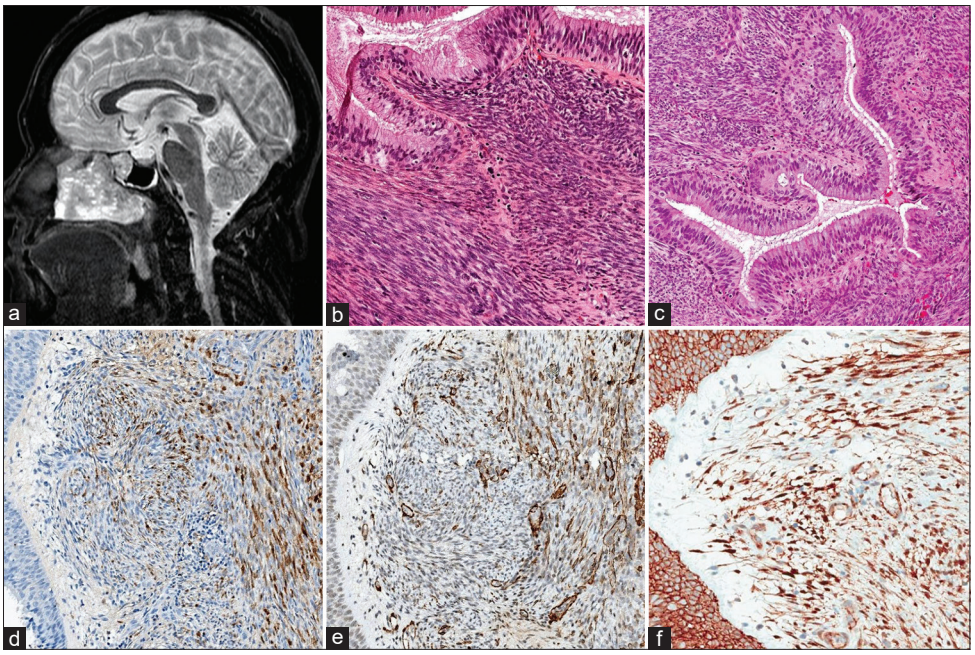

Figure 1: Case2 MRI T1 GD (a), fascicular pattern (b; H and E, ×100), entrapped epithelium (c; H and E, ×100), S100 (d; ×100), SMA (e; ×100) and nuclear *B*-catenin (f; ×200)

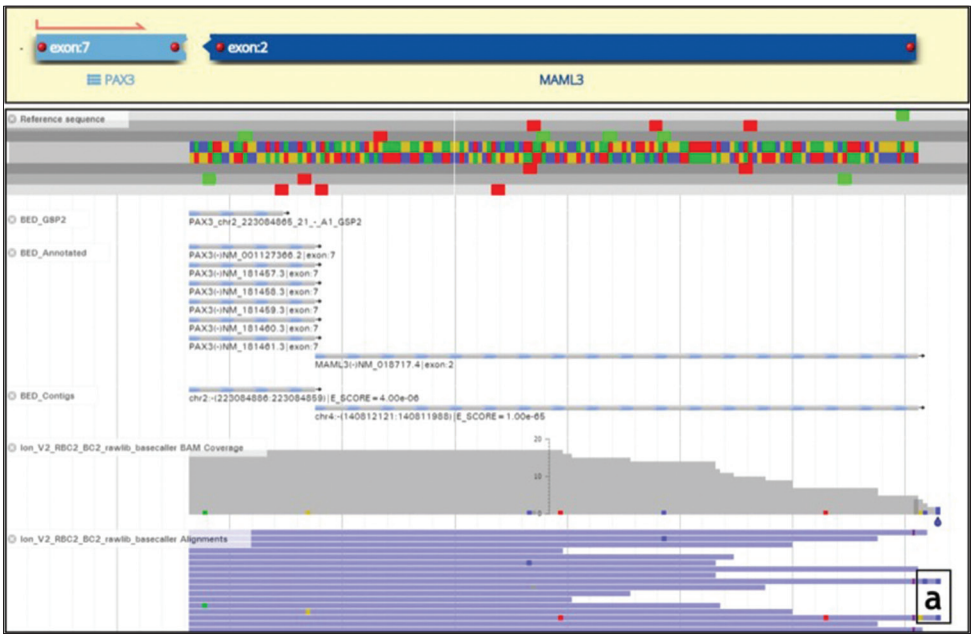

Figure 2: Fusion gene PAX3 (exon7)-MAML3 (exon2) (*PAX3* Transcript: NM_181457.3, *MAML3* Transcript: NM_018717.4) and the NGS reads spanning the breakpoint of the fusion in case 1

markers.[1,2,9,10] A panel approach is recommended where the combined expression of SMA, S100, and *B*-catenin strongly favors BSNS. If SS cannot be completely ruled out, detection of *SYT-SSX* fusion provides a definitive diagnosis of SS.

Low-grade malignant peripheral nerve sheath tumor (MPNST) of the sinonasal tract is thought to have represented underrecognized BSNS before the description of this entity.[1] Features of MPNST are perivascular condensation of tumor cells, alternation of hypercellular and hypocellular areas, proven origin from a nerve, and onset in neurofibromatosis type 1 patient. Mitotic activity, nuclear atypia, necrosis, and pleomorphism are typically absent in low-grade MPNST. MPNST is focally positive for S100 and can express muscle markers even in the absence of frank rhabdomyoblastic differentiation. SOX10 is a variable expressed in MPNST and nuclear *B*-catenin

is consistently nonexpressed. In this specific differential diagnosis setting, a combination of SMA, S100, and nuclear *B*-catenin positivity and SOX10 negativity supports a BSNS diagnosis.

In adults, spindle cell rhabdomyosarcoma frequently affects the head–and-neck region. It may show spindle cell morphology reminiscent to that of BSNS. Spindle cell rhabdomyosarcoma may be focally positive for S100, but a diffuse expression of desmin and myogenin are diagnostic.

Spindle cell melanoma enters the differential diagnosis of BSNS. Consistent lack of SOX 10, and other melanocytic markers in BSNS, helps rule out spindle cell melanoma.

In summary, this report adds to the list of molecularly confirmed BSNS. Our cases show the classical morphology and immunohistochemical characteristics reported in the literature for this sinonasal entity.

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Conflicts of interest
There are no conflicts of interest.

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