Head and Neck Pathology (2023) 17:826–831
https://doi.org/10.1007/s12105-023-01566-6

CASE REPORT

Biphenotypic Sinonasal Sarcoma with a Novel *PAX7*::*PPARGC1* Fusion: Expanding the Spectrum of Gene Fusions Beyond the *PAX3* Gene

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Received: 20 May 2023 / Accepted: 11 June 2023 / Published online: 28 June 2023

Abstract

Biphenotypic sinonasal sarcoma (BSNS) is a rare low-grade malignancy occurring in the sinonasal tract that is characterized by dual neural and myogenic differentiation. Rearrangements involving the *PAX3* gene, usually with *MAML3*, are a hallmark of this tumor type and their identification are useful for diagnosis. Rarely, a *MAML3* rearrangement without associated *PAX3* rearrangement has been described. Other gene fusions have not been previously reported. Herein, we report a 22 year-old woman with a BSNS harboring a novel gene fusion involving the *PAX7* gene (specifically *PAX7*::*PPARGC1A*), which is a paralogue of *PAX3*. The histologic features of the tumor were typical with two exceptions: a lack of entrapment of surface respiratory mucosa and no hemangiopericytoma-like vasculature. Immunophenotypically, the tumor was notably negative for smooth muscle actin, which is usually positive in BSNS. However, the classic S100 protein-positive, SOX10-negative staining pattern was present. In addition, the tumor was positive for desmin and MyoD1 but negative for myogenin, a pattern that is common among BSNS with variant fusions. Awareness of the possibility of *PAX7* gene fusions in BSNS is important as it may aid in the diagnosis of *PAX3* fusion negative tumors.

Keywords Biphenotypic sinonasal sarcoma · *PAX3* · *PAX7* · *PPARGC1* · Gene fusion · Gene rearrangement

Introduction

Biphenotypic sinonasal sarcoma (BSNS) is rare sinonasal malignancy that was first described in 2012 as a "low-grade sinonasal sarcoma with neural and myogenic features" due the presence of dual neural and smooth muscle marker positivity by immunohistochemistry [1]. The entity was subsequently incorporated into the 4th Edition of the WHO classification of head and neck tumors in 2017 and termed biphenotypic sinonasal sarcoma [2]. BSNS is clinically a low-grade sarcoma that can be locally aggressive but thus far is non-metastasizing with over 100 cases reported in the literature [3–6]. Rarely, high-grade transformation can occur in the form of rhabdomyosarcoma [7–9]. The majority of tumors harbor recurrent gene fusions involving the *PAX3* gene, most frequently a *PAX3::MAML3* fusion, which can be useful to confirm the diagnosis [10]. In a minority of cases, alternative *PAX3* fusion partners have been described and rarely a *MAML3* rearrangement may occur in the absence of *PAX3* rearrangement, and the fusion partner is unknown [4, 11–15]. Gene fusions other than in *PAX3* and/or *MAML3* have not been identified in BSNS. We herein report, to our best knowledge, the first case of biphenotypic sinonasal sarcoma with a novel *PAX7::PPARGC1A* fusion.

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Case Description

Clinical Presentation

A 22-year-old woman without significant medical or surgical history presented to the emergency department with 2 week history of vision loss and headaches. The patient also noted an 8 month history of hyposmia and nasal obstruction that she initially attributed to COVID-19 infection. A month prior to presentation, she was seen by her primary care physician for rhinorrhea, facial pressure, and headaches, not responding to over-the-counter nasal sprays. She denied facial numbness, weakness, hoarseness, dysphagia, or dyspnea.

On physical examination, a large mass obstructing left nasal cavity was noted. No nasal discharge or drainage was seen. Magnetic resonance imaging (MRI) revealed a 7.8 cm enhancing mass in the right and left nasal cavity, ethmoid and sphenoid sinuses and left maxillary sinus with extension into the anterior cranial fossa and mass effect on the bilateral frontal lobes and the corpus callosum. The tumor also extended into the right and left orbits with mass effect on the medial rectus musculature and likely involvement of both optic nerves (Fig. 1). A clinical differential diagnosis included olfactory neuroblastoma and meningioma, among other tumor types. The patient initially underwent bedside endoscopic intranasal biopsy that was not diagnostic, and subsequently a larger biopsy and limited debulking surgery. A CT scan of the chest, abdomen, and pelvis was negative for metastatic disease. She was then treated with neoadjuvant doxorubicin and trabectedin chemotherapy. Restaging MRIs after five months of chemotherapy demonstrated only a minor but not meaningful response. Therefore, she underwent a combined open and endoscopic craniofacial resection with subtotal tumor resection. Postoperative MRI demonstrated nodular enhancement in the anterior cranial fossa measuring 2.5 cm on the left and 0.9 cm on the right that was suspicious for residual tumor. Adjuvant proton beam radiation was then administered. The patient is alive with disease 10 months after initial diagnosis.

Histopathology

Histologic examination showed a monotonous spindle cell neoplasm with a prominent fascicular growth pattern and variably hypo- and hypercellular regions, although the latter predominated (Fig. 2). The tumor was fairly well-demarcated from the overlying mucosa. However, it was poorly circumscribed and infiltrative into underlying bone. The tumor cells had ovoid to elongated, hyperchromatic nuclei and scant cytoplasm with indistinct cell borders. There was minimal mitotic activity (< 1 per 10 high-power fields) and no atypical mitoses or necrosis were present. Hemangiopericytoma-like vasculature was notably absent. Immunohistochemistry showed the tumor cells to have scattered positivity for S100 protein, rare positivity for desmin and patchy positivity for MyoD1 (Fig. 3). Smooth muscle actin (SMA), myogenin, SOX10, cytokeratin, epithelial membrane antigen, beta-catenin, CD34 and STAT6 were negative. The presence of MyoD1 expression raised diagnostic consideration of

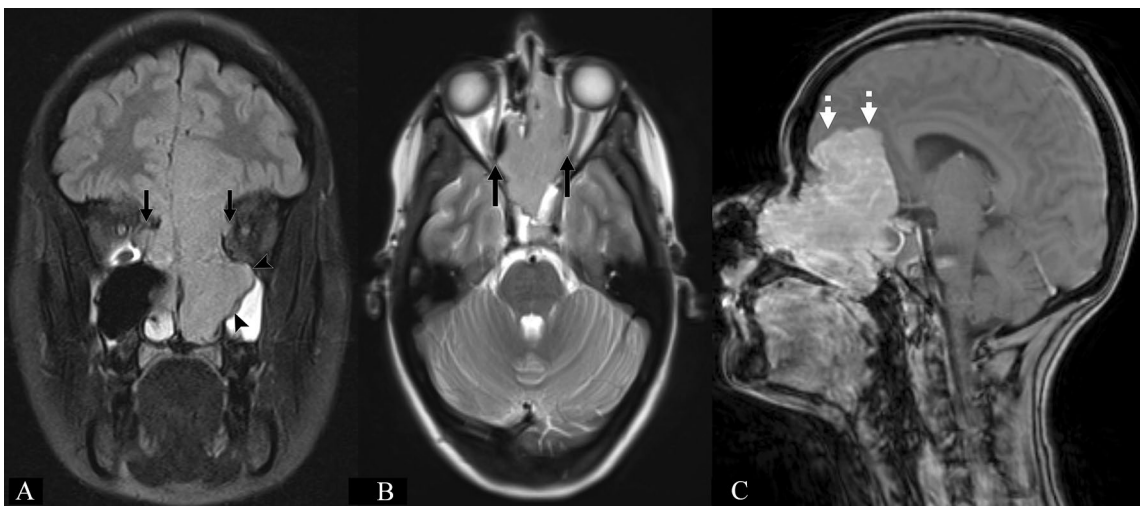

Fig. 1 Coronal FLAIR image from the MRI (**A**) shows a large sinonasal mass that extends into the bilateral extraconal orbit (arrows) as well as into the left maxillary sinus (arrowheads) and anterior cranial fossa. Axial turbo spin echo T2-weighted image (**B**) shows an intermediate intensity extra-axial mass centered in the sinonasal cavity that extends into the extraconal orbit bilaterally with mass effect on the medial rectus musculature (arrows). Sagittal T1-weighted image with contrast (**C**) demonstrates the avid enhancement of the mass which also extends into the anterior cranial fossa and exerts mass effect on the frontal lobes and corpus callosum (dashed arrow)

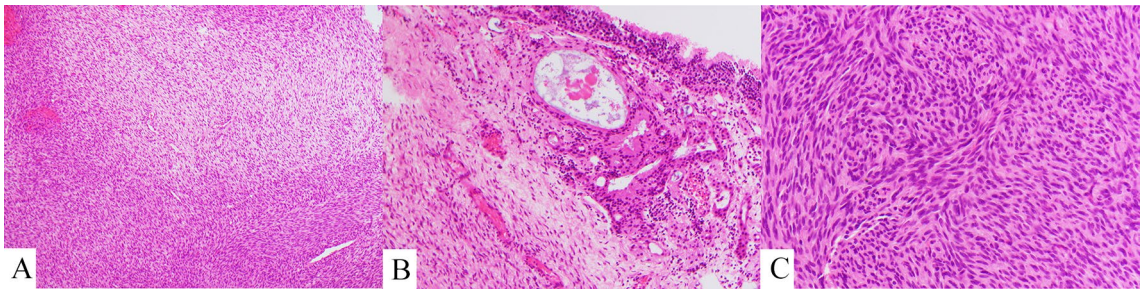

Fig. 2 Histologic sections of the biphenotypic sinonasal sarcoma (BSNS) showed variable hypo- (top) and hypercellular (bottom) regions but was predominantly hypercellular (**A**). The tumor was well demarcated from the overlying respiratory mucosa (**B**) and lacked mucosa entrapment that is often present in BSNS. Hypercellular areas of the tumor displayed a prominent fascicular growth pattern that is characteristic of BSNS (**C**)

a spindle cell rhabdomyosarcoma. The bland tumor cytology combined with the lack of mitotic activity, rhabdomyoblasts or sclerotic stroma, and the immunophenotype (S100 positive, myogenin negative, desmin rare positive) argued against this possibility. BSNS was favored.

Next Generation Sequencing (NGS)

Although a diagnosis of BSNS was suspected, the biopsy specimen was sent for NGS due to the presence of atypical features, namely the absence of SMA positivity, lack of tumor entrapment of hyperplastic surface respiratory mucosa and no hemangiopericytoma-like vasculature. The clinically available sarcoma targeted gene fusion/rearrangement panel (SARCP), which identifies fusions in 138 genes known to be rearranged in sarcomas, was performed at the Mayo Clinic on the formalin-fixed paraffin embedded tissue block (https://www.mayocliniclabs.com/test-catalog/Overview/606427). A novel fusion between exon 7 of *PAX7* and exon 2 of *PPARGC1A* genes was identified, which was also independently confirmed by reverse transcriptase PCR at the Mayo Clinic.

Discussion

Classic BSNS occurs exclusively in the sinonasal tract and is primarily seen in middle aged adults with an age range of 24–85 years [1, 4–6]. Our patient is the youngest at 22 years old among all the cases of BSNS described in the English language literature so far. There is a striking female predominance and the nasal cavity and ethmoid sinus are the most common involved sites. Histologically, BSNS is characterized by a cellular proliferation of uniform, mildly atypical spindle cells with ovoid to elongated hyperchromatic nuclei. The tumor cells are often arranged in fascicles with an occasional herringbone pattern. Proliferation of surface respiratory epithelium and entrapment by the tumor cells in the form of small glands to cystically dilated spaces is also commonly seen. Another feature described in BSNS is presence of staghorn hemangiopericytoma-like vessels. These latter two features were not present in our patient's tumor but the histologic features were otherwise typical. S100 protein is characteristically positive, while SOX10 is negative [16]. SMA is usually, but not always, expressed, although it was absent in our case. A subset is positive for desmin and skeletal muscle markers such as myogenin and MyoD1 [4, 14].

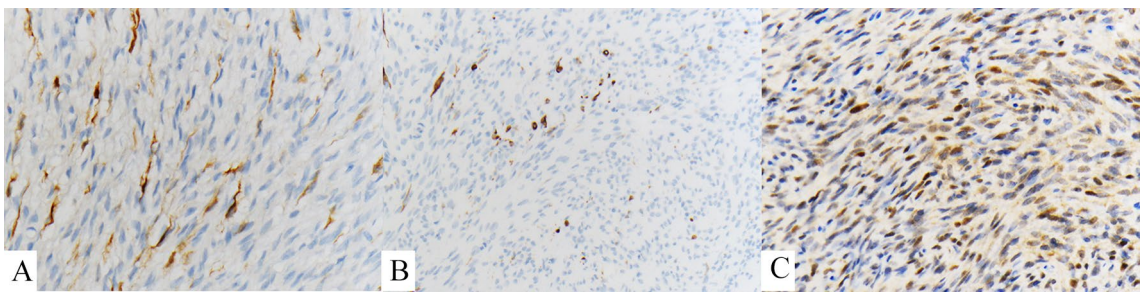

Fig. 3 The tumor cells showed scattered positivity for S100 protein (**A**), rare positivity for desmin (**B**) and had patchy positivity for MyoD1 by immunohistochemistry (**C**)

There are a variety of other benign and malignant mesenchymal neoplasms that have either overlapping morphologic or immunophenotypic features with BSNS and, thus, the diagnosis can be challenging, especially on small biopsy. Most notably these include glomangiopericytoma, solitary fibrous tumor, and monophasic synovial sarcoma. Making a correct diagnosis is important due to the differences in their biologic behaviors and treatment options. Detection of a *PAX3* gene rearrangement can solidify the diagnosis of BSNS in challenging cases.

PAX3::MAML3 fusions occur in more than half to 90% of BSNSs with the majority of the remaining tumors harboring alternative *PAX3* rearrangements (including *PAX3::FOXO1*, *PAX3::NCOA1, PAX3::NCOA2,* and *PAX3::WWTR1*) or, rarely, a *MAML3* fusion with a non-*PAX3* unknown fusion partner has been described [4, 14, 15]. Less than 10% are negative for *PAX3* fusions altogether [4, 14]. Patients with alternate fusions tend to be younger and, while they show variable expression of desmin and MyoD1, they usually lack myogenin [14]. Likewise, our patient with a novel, non-*PAX3* or *MAML3* fusion is the youngest reported patient with BSNS and showed a similar MyoD1 and desmin-positive, myogenin-negative immunophenotype as has been reported in other variant fusion cases. Other clinical differences between tumors with conventional and alternative fusions have not been detected.

Non-*PAX3* or *MAML3* rearrangements have not previously been reported in BSNS with the exception of an unusual oropharyngeal sarcoma found to have a *RREB1::MRTFB* (formerly *RREB1::MKL2*) fusion [17]. *RREB1::MRTFB* is the same fusion present in ectomesenchymal chondromyxoid tumors of the tongue [18]. The reported oropharyngeal tumor, however, had morphologic and immunophenotypic overlap (S100 protein, SMA, desmin, and myogenin positive) with BSNS and was termed 'biphenotypic oropharyngeal sarcoma' [17]. Our case with a *PAX7::PPARGC1A* fusion is the first example of a non-*PAX3* or *MAML3* fusion in a BSNS of the sinonasal tract. It is also the first example of a *PAX7* rearranged BSNS, an unsurprising occurrence as *PAX3* and *PAX7* are related genes.

PAX3 is a member of the PAX family of transcription factors and plays an important role in the development of skeletal muscle and neural crest tissue [19–21]. PAX7 is also a PAX family transcription factor and plays a crucial role in the formation and differentiation of skeletal muscle precursor cells during embryonic development [19, 21]. PAX3 and PAX7 are paralogues and both are also important regulators of craniofacial and nasal structure development [22, 23]. Either *PAX3* or *PAX7* genes are rearranged in alveolar rhabdomyosarcoma, thus, it is not surprising that PAX7 rearrangements, in addition to *PAX3* rearrangements, could also occur in BSNS [21, 24]. Indeed, PAX7 expression by immunohistochemistry has been demonstrated in at least one BSNS, a case that harbored the most common *PAX3::MAML3* fusion [25]. PAX7 expression in BSNS may be related to rhabdomyoblastic differentiation that is present in a subset of these tumors. PAX7 is a transcriptional regulator of muscle progenitor cells and is a marker of skeletal muscle differentiation. It is generally expressed in rhabdomyosarcomas and other tumors with rhabdomyosarcomatous differentiation [26, 27].

The *PAX7* fusion identified in our patient is a novel fusion that has not been previously reported in any tumor type including BSNS. *PPARGC1A*, the *PAX7* fusion partner, is a primary driver of mitochondrial biogenesis [28]. Gene fusions involving *PPARGC1A* are very rare. A spindle cell rhabdomyosarcoma of the oral cavity was reported to have a *PPARGC1A::VGGLL3* fusion and an *EGFR::PPARGC1A* fusion was found in a cell line from a cutaneous squamous cell carcinoma [29, 30].

It should be noted that rhabdomyosarcoma, particularly the spindle cell/sclerosining variant, shares some features with BSNS but they have important clinical and pathologic differences. Both spindle cell/sclerosing rhabdomyosarcoma and BSNS show rhabdomyosarcomatous differentiation, occasionally *NCOA2* gene rearrangements, and now rarely *PPARGC1A* gene rearrangements, albeit with different fusion partners [29, 31, 32]. Spindle cell/sclerosing rhabdomyosarcomas may also, like BSNS, have a fascicular or herringbone growth pattern but shows greater morphologic heterogeneity, mitotic activity, and nuclear atypia than is present in BSNS [33]. In addition, areas of primitive round cells, rhabdomyoblasts and stromal sclerosis/hyalinization may be present, features that are not found in BSNS [33]. Immunophenotypically, spindle cell/sclerosing rhabdomyosarcoma is diffusely desmin positive and lacks S100 protein expression. Our case of BSNS was notably S100 protein positive, as is typical of BSNS, and displayed only rare desmin immunoreactivity. The prognosis of spindle cell/sclerosing rhabdomyosarcoma is variable, with *MyoD1*-rearranged tumors behaving more aggressively, whereas BSNS is associated with favorable clinical outcomes and no metastases [29, 32, 34–36]. Nevertheless, it is possible that BSNS and spindle cell/sclerosing rhabdomyosarcoma are related tumor types.

PAX3 gene rearrangements, a hallmark of BSNS, or *PAX7* gene rearrangements have not been reported in spindle cell/sclerosing rhabdomyosarcoma but are classically found in alveolar rhabdomyosarcomas [24]. Although the fusion partners are usually different, the *PAX3::FOXO1* gene fusion, which is common in alveolar rhabdomyosarcoma, may also rarely occur in BSNS. Despite molecular overlap, alveolar rhabdomyosarcoma and BSNS are quite different tumor types. The former is a high-grade round cell sarcoma, whereas BSNS is a low-grade spindle cell neoplasm.

In summary, we report a novel fusion involving the *PAX7* and *PPARGC1A* genes in BSNS, which further strengthens the molecular ties between BSNS and rhabdomyosarcoma. Although they are clinically and pathologically distinct tumor types, both BSNS and alveolar rhabdomyosarcoma may have rearrangements involving *PAX3* (including *PAX3::FOXO1*) and now also *PAX7*. Prior to this case, fusions in BSNS almost exclusively involved *PAX3* and rarely *MAML3* with a non-*PAX3* unknown fusion partner. As such, evaluation for *PAX3* rearrangements, often by fluorescence in situ hybridization or immunohistochemistry, has become an important diagnostic tool in BSNS [37]. In light of the current case, *PAX7* rearrangements should also be investigated in *PAX3*-negative tumors.

Author Contributions SB and RDC wrote the main manuscript text. CAR prepared Fig. 1. RDC prepared Figs. 2 and 3. All authors reviewed and edited the manuscript. All authors contributed to this case report and have read and approved the manuscript.

Funding There are no sources of funding to disclose.

Declarations

Conflict of interest Rebecca D. Chernock has a non-financial relationship with Caris Life Sciences as a member of their Precision Oncology Alliance and is a member of the Steering Committee for a Phase III clinical trial of neoadjuvant Pembrolizumab in surgically resectable, locally advanced head and neck squamous cell carcinoma (MK-3475-689), Merck & Co., Inc. Brian A. Van Tine has research grants or contracts from Pfizer, Merck, Tracon Pharm, GSK and Polaris; a has a license for a patent from Accuronix Therapeutics; received consulting fees from Cytokinetics Inc, Bayer, Deciphera Pharmaceuticals, Daiichi Sanko Inc, EcoR1, Advenchen, Putnam, Salarius Pharmaceuticals Inc., Boxer Capital LLC, Acuta Capital Partners, LLC and Aadi; received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Iterion Therapeutics, Inc. and Total Health Conference; received payment of expert testimony from Anderson and Reynolds PLC; received support for attending meetings or travel from Adaptimmune; has planned, issued or pending patents on ALEX3102 and the use of ME1 as a biomarker; participated on data safety monitoring or advisory boards for Apexigen, INC, Daiichi Sankyo, Epizyme, Bayer US Medical Affairs Oncology, PTC Therapuetics, Aadi Biosciences, Boehringer Ingelheim, Agenus, Regeneron Pharmaceuticals, Advenchen, EcoR1 Captial, LLC and Curis; and is a board member at Polaris.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The institutional review board (IRB) determined that no human research was performed for this descriptive case report.

Informed Consent 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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