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High-Grade Biphenotypic Sinonasal Sarcoma: A Case Report

Sukaina Hasnie[1] Chad Glenn[1] Jo E. G. Peterson[2] Edward T. El Rassi[2] Kibwei A. McKinney[1]

[1] Department of Otolaryngology, University of Oklahoma, Oklahoma City, Oklahoma, United States
[2] Department of Otolaryngology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, United States

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Address for correspondence Sukaina Hasnie, MD, Department of Otolaryngology Head and Neck Surgery, University of Oklahoma Health Sciences Center, Andrews Academic Tower, Suite 1400, 800 Stanton L. Young Boulevard, Oklahoma City, OK 73104, United States (e-mail: Sukaina-hasnie@ouhsc.edu).

Abstract

Introduction Biphenotypic sinonasal sarcoma (BSNS) is a recently found entity that first described by Lewis et al. It was then added to the 4th edition of the World Health Organization (WHO) of head and neck tumors in 2012. BSNS has been described as a rare low-grade sarcoma arising in the upper sinonasal tract. It is believed that in the past, BSNS was, likely, previously diagnosed as other low-grade or benign malignancies. Fibrosarcoma, leiomyosarcoma, and peripheral nerve sheath tumors, all fall within the differential diagnosis of BSNS. However, BSNS is unlike other mesenchymal sinonasal tumors, as it displays both neural and myogenic differentiation. BSNS has thus far been recognized in only a hand full of case reports, all of which have reported similar morphologic features of a low-grade soft tissue tumor with neural involvement arising from the nasal cavity or ethmoid air cells in middle aged individuals. In fact, being low-grade sarcoma became such a hallmark characteristic of this tumor that it even received the name low-grade sinonasal sarcoma with neural and myogenic features or LGSSNMF.

Case Presentation We present, however, for the first time, a high-grade differentiation of BSNS in an otherwise healthy 72-year-old female. The patient was referred from an outside ENT (ear, nose, and throat) after pathology from a presumed polypectomy returned positive for a BSNS. Initial imaging revealed erosion through the bilateral lamina papyracea, anterior cranial fossa floor, and posterior table of the frontal sinus. She then underwent a combined endoscopic and bicoronal open approach for resection of the skull base lesion that was found to encompass the entirety of the sinonasal cavities bilaterally. Postoperatively, the patient underwent significant complications including infection of the pericranial flap, pneumocephalus, and eventually death.

Discussion As BSNS is a fairly new entity, currently there has only been four case series conducted, each identifying features of a low-grade sarcoma with both myogenic and neural differentiation. Histologically, BSNS has monophasic spindle cells with uniform, elongated nuclei with scant cytoplasm between benign proliferations of surface-type respiratory epithelium, with a low mitotic rate. Our case, however, revealed

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pleomorphic hyperchromatic cells with high mitotic activity and necrosis with invasion of bone, staging it as high grade. Immunohistochemistry also differed from the previously reported standards. This case describes a new category for BSNS which may change the differential diagnosis, management, and surgical recommendations that are currently utilized for this skull base neoplasm.

Introduction

Biphenotypic sinonasal sarcoma (BSNS) is a recently described pathologic entity with the nomenclature first being proposed by Lewis et al in 2012.[1] It was then added to the 4th edition of the World Health Organization (WHO) of head and neck tumors in 2012.[2] BSNS is characterized as a rare low-grade sarcoma most commonly arising in the upper sinonasal tract of middle-aged individuals with a relatively favorable prognosis.[3] It is believed that in the past, BSNS was, likely, previously characterized as other low-grade or benign malignancies. Fibrosarcomas, leiomyosarcomas, and nerve sheath tumors, all fall within the differential of BSNS.[4,5] BSNS differs from these other mesenchymal sinonasal tumors in that it demonstrates dual differentiation, expressing both muscle and nerve markers, as well as frequent PAX3 translocations. These tumors were historically identified in pathology literature as a low-grade sinonasal sarcoma with neural and myogenic features (LGSSNMF). To date, reports of BSNS have been limited to a handful of cases, each describing similar morphologic features of a low-grade soft tissue tumor with dual differentiation arising from the nasal cavity or ethmoid air cells in middle-aged individuals. To the best of our knowledge, this report presents the first known case of BSNS with high-grade transformation or dedifferentiation.

Case Presentation

The patient is a 72-year-old female with a 2-year history of progressive nasal obstruction with episodic epistaxis and facial pressure/headaches, as well as decreased sense of smell. She initially presented to a community otolaryngologist and underwent medical treatment including antibiotics and intranasal corticosteroids for presumed chronic rhinosinusitis with nasal polyposis. Due to a lack of improvement in symptoms, she then underwent endoscopic sinus surgery where surgical biopsy demonstrated a classic BSNS. The patient was subsequently referred to the University of Oklahoma Health Science Center (OUHSC) for definitive evaluation and treatment.

When she was initially seen at OUHSC, her primary symptom was a periorbital headache that extended posteriorly to the occipital region. She additionally endorsed recurrent, self-limiting bouts of epistaxis, as well as a decreased sense of smell. She denied diplopia or visual changes. She also denied facial numbness.

On physical examination, there was evidence of a central 1.0 cm $\times$ 0.5 cm bony defect of the anterior table of the frontal sinus that was tender to palpation. No cranial neuropathies, visual defects, or lymphadenopathy were noted. Nasal endoscopy revealed a friable, polypoid lesion emanating from the right middle meatus with surrounding crusting and mucopurulent drainage.

Imaging

Computed Tomography

The initial preoperative computed tomography (CT) performed prior to endoscopic sinus surgery demonstrated complete opacification of the right maxillary sinus, right ethmoidal air cells, bilateral frontal sinuses, and blocked osteomeatal complex with a leftward septal deviation (►**Fig. 1**).

A repeat CT with contrast, obtained upon referral to OUHSC, revealed an enhancing sinonasal mass with erosion through the bilateral lamina papyracea, anterior cranial fossa floor, and posterior table of the frontal sinus. There was no evidence of intraconal orbital involvement.

Magnetic Resonance Imaging

On magnetic resonance imaging (MRI), an infiltrative tumor was present with bilateral intraorbital and intracranial extension (►**Fig. 2**). Orbital involvement appeared to be limited to the extraconal space sparing the extraocular musculature and intraconal structures. Intracranial extension was present along the anterior cranial fossa floor bilaterally, more extensive on the right than left, with possibly reactive dural thickening but no evidence of brain parenchymal involvement.

Surgical Details

The surgical approach included a combined endoscopic craniofacial and bicoronal approach for resection of the base of skull lesion. Stereotactic image guidance was used throughout the entire procedure. The mass was noted to encompass the entirety of the sinonasal cavities bilaterally but elevated freely off the nasal floor, septum, right maxillary sinus, and the bilateral lateral nasal walls and the lamina papyracea. There was erosion of the right lacrimal crest and erosion of the right aspect of the posterior table, extending into the midline with transdural extension. The tumor extended posteriorly along the ethmoid skull base, back to the level of the face of the right sphenoid sinus, without transcranial extension. Externally, the anterior table defect had increased in size to 1.5 cm $\times$ 1.0 cm, with involvement of the prefrontal soft tissues. Intradural elevation of the frontal lobe was performed, and a gross total resection was achieved.

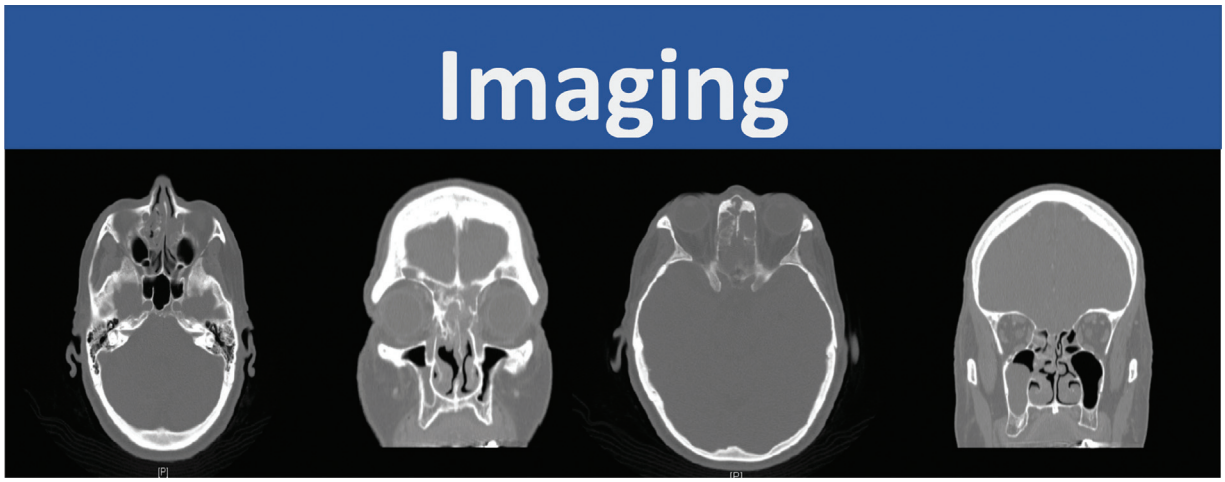

Fig. 1 CT findings included enhancing sinonasal mass with erosion through the bilateral lamina papyracea, anterior cranial fossa floor, and posterior table of the frontal sinus. CT, computed tomography.

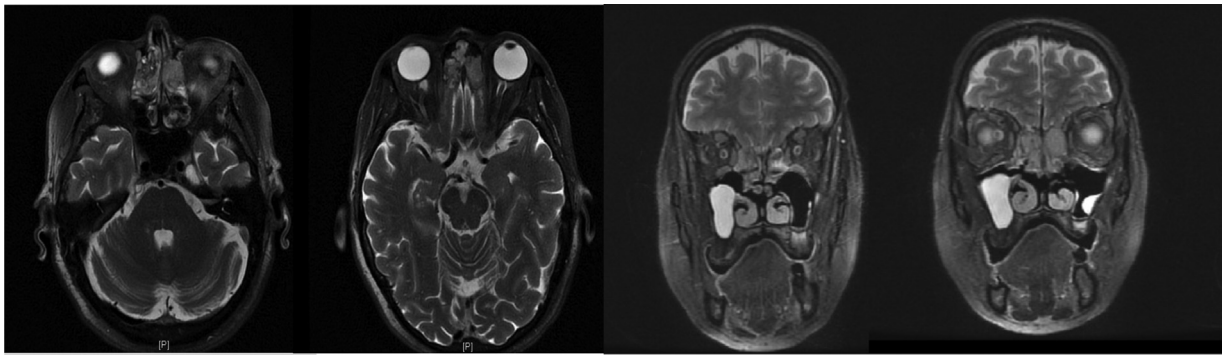

Fig. 2 MRI findings were pertinent for extension into bilateral orbits without involvement of the rectus muscles or intraconal structures and intracranial extension along the anterior cranial fossa without brain parenchymal involvement. MRI, magnetic resonance imaging.

The procedure began with the endoscopic craniofacial approach. Multiple specimens were sent from the anterior aspect of the mass for frozen pathology. The dissection went from anterior to posterior and the tumor was freely elevated off nasal floor, septum, and inferior turbinate. Due to the extent of the tumor throughout the nasal cavity and maxillary sinus, it was removed in a piecemeal fashion rather than en bloc. For access, the middle turbinate was sacrificed, and the tumor was resected from the posterior ethmoid, sphenoid, and frontal sinuses up to the level of the skull base and laterally, to the level of the orbital apex. A Draf 3 frontal sinusotomy was performed. The resulting defect permitted visualization of the residual tumor up to the level of the frontal convexity. Because there was evidence of transcranial involvement through the posterior table, the decision was made to proceed with craniotomy through a bicoronal approach. During the course of this approach, there was evidence of central thinning of the pericranial flap due to mass effect. The flap was otherwise uninvolved and elevated-off of the anterior face of the mass. A gross total resection was achieved.

A multilayer repair was then performed. The dural defect was closed with Durepair (Medtronic) and secured with Anastoclips (LeMaitre Vascular). Tensor fascia lata was harvested and placed intracranially, spanning the distance between the orbital roof on each side. The pericranial flap was placed inferior to the tensor fascia lata graft and bolstered with dural sealant, Nasopore (Stryker), and 10-cm Merocel (Medtronic) packing bilaterally along the floor of the nose. The bone of the anterior table was then placed back into its native position and secured with titanium plates and screws. The patient tolerated the procedure well without complications and was admitted to the neuro–intensive care unit (ICU) postoperatively.

Postoperative Course

On postoperative day 2, the patient was noted to have mental status changes due to a small left frontal intrapranchymal hemorrhage and subarachnoid hemorrhage. This was managed conservatively with serial imaging. No progression was noted, and the patient's mental status returned to baseline. She was then discharged on postoperative day 5 with nasal packing in place for 2 weeks. At her first postoperative appointment, she reported doing well without concerns for a cerebrospinal fluid (CSF) leak, her packing was removed, and she underwent sinonasal debridement. One month following surgery, she presented with periorbital and frontal swelling, rhinorrhea, and mental status changes. She was taken back to the operating room and found to have necrosis

of the pericranial flap with mucopurulence emanating from the cranialized frontal sinus. There was no evidence of a CSF leak at that time. Another repair was performed using abdominal fat and bilateral extended nasoseptal flaps. She presented again 3 months from resection and 2 months from revision with pneumocephalus secondary to dissolution of skull base repair and subsequent communication between the nasal cavity and intracranial space. Consideration was given to performing a free flap, but this was contraindicated due to the onset of multisystem organ failure. The patient ultimately died 4.5 months after her resection from an acute coronary event. No signs of tumor recurrence were noted throughout the postoperative course or prior to death.

Pathology

The original biopsy demonstrated a monomorphic proliferation of spindled cells in a background of myxoid changes (►**Fig. 3**). Nuclear atypia, mitotic figures, and/or necrosis were not seen. The tumor cells demonstrated focal immunoreactivity to muscle markers (smooth muscle actin, desmin, and myogenin) and was also focally immunoreactive for S-100 protein, a marker of neuronal differentiation. The resection specimen demonstrated some regions that were histologically similar to the previous biopsy; however, the majority of the resection was comprised of plump and pleomorphic hyperchromatic cells with frequent mitotic activity and necrosis, all features of a high-grade neoplasm. Fluorescence in situ hybridization (FISH) evaluation of the tumor demonstrated the presence of a *PAX3* translocation on gene 2q36.1, with 94.5% positivity in all cells. Further molecular analysis noted copy number alterations of 9p and 22, confirming the high-grade phenotype. The high-grade component of this tumor demonstrated focal muscle differentiation with occasional immunoreactivity for myogenin and desmin but no longer retained the neuronal differentiation.

Discussion

Sarcomas of the head and neck are rare, accounting for only 5 to 15% of all soft tissue sarcomas overall.[6] Sinonasal sarcomas are even more uncommon accounting for less than 10% of all head and neck sarcomas. BSNS is a newly described entity characterized by the presence of both neural and myogenic differentiation and frequently harboring *PAX3* translocations. Prior to recognizing BSNS as a distinct entity, these cases may have been diagnosed as another in the differential including fibrosarcoma, malignant peripheral nerve sheath tumor (MPNST), myofibrosarcoma, rhabdomyosarcoma, angiosarcoma, leiomyosarcoma, and/or low-grade nerve sheath tumor[5].

BSNS is histologically characterized by monophasic spindle cells with uniform, elongated nuclei with scant cytoplasm in a background of benign proliferations of surface-type respiratory epithelium.[3,7] It often displays a hemangiopericytoma-like vascular pattern,[3,5] while lacking high-grade features such as

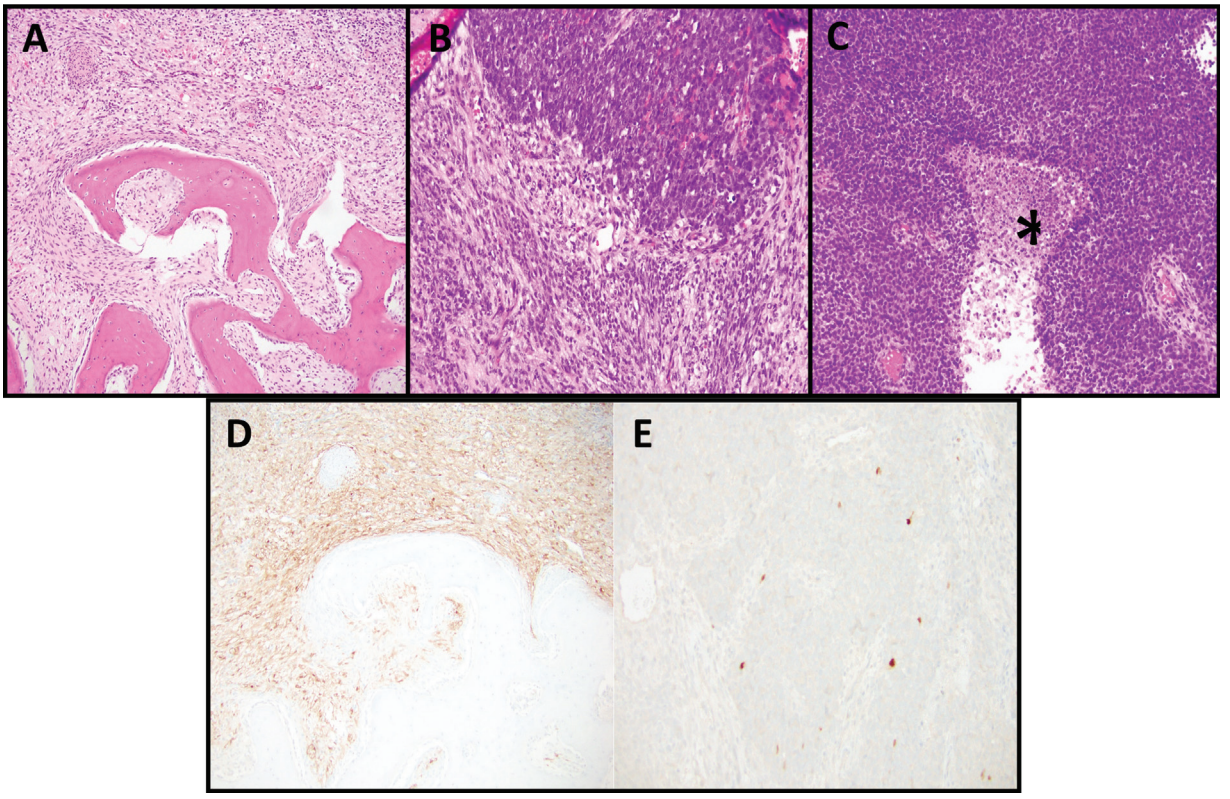

Fig. 3 (**A**) The low-grade component can be seen infiltrating pink pieces of bone (H&E, ×100). (**B**) The interface between the low-grade component (bottom), and the high-grade component (upper, H&E, ×200). (**C**) Necrosis* in the high-grade component (H&E, ×200). (**D**) Diffuse S-100 protein staining in the low-grade component (×100). (**E**) Focal myogenin staining in the high-grade component (×200). H&E, hematoxylin and eosin.

brisk mitotic activity, nuclear pleomorphism, or necrosis. Most tumors are immunoreactive for smooth muscle actin (SMA), muscle-specific actin (MSA), and S-100 protein, and nonreactive for cytokeratin, desmin, and CD34[4].

Initially, BSNS was described as having a t(2;4)(q35;q31) recurrent translocation resulting in a *PAX3-MAML3* fusion.[3,6] This specific translocation stimulates a biphenotypic transcription of dual neuroectoderm and myogenic differentiation. The PAX family of genes plays a role in tissue and organ development during embryogenesis. *PAX3* specifically plays a role in determining the fate of melanocytic, neural, and skeletal muscle differentiation.[3] It also regulates normal myogenesis and postnatal muscular regeneration. Recently, more fusion partners with the *PAX3* gene have been noted such as *FOXO1*, *NCOA1*, and *NCOA2*. More recently another partner has been identified, WWTRA.[1] In some cases, the fusion partner with *PAX3* was not identified. *MAML3*, *FOXO1*, *NCOA1*, and *NCOA2* proteins are all structurally and functionally similar.[1,4,8] One of the larger case series that evaluated 44 cases reported the following ratio of translocations: *PAX3-MAML3*, 55% (24/44), *PAX3* with *FOXO1*, *NCOA1*, or *NCOA2* fusions, 25 (11/44), and 9% without an identifiable fusion.[1,3,8]

At the time of this publication, four case series have been published of BSNS.[1] Like other malignancies of the head and neck, BSNS patients usually present with sinus/facial pain, nasal obstruction, epistaxis, proptosis, or cranial nerve palsies. It is often found in middle-aged patients with a mean age of 52 years, and with a predilection toward females with a ratio of 3:1.[6,7] Case studies describe the primary location as either the nasal cavity (54%), ethmoid sinus (57%), or a combination of the two sites.[5] This is in contradistinction to other sinonasal carcinomas in which involvement of the ethmoids occurs in less than 10 to 15%.[1] As expected from its proximity to the skull base, these tumors have shown extension to the orbit and anterior cranial fossa. Orbital and cranial extension is seen in 25 and 10% of cases, respectively.[4,6] Local reoccurrences have been reported in 40 to 50% of cases based on case series; however, distant metastases are unreported.[4] There is currently no consensus on the roll off postoperative adjuvant radiation or primary radiotherapy in the management of these tumors. Some physicians recommend postoperative radiation for positive or close surgical margins or in those with perineural spread. Primary radiation is only given for palliative treatment. In only one reported case has been reported death secondary to complications associated with reoccurrence with persistent intracranial involvement.[12]

The pathology in our case initially was consistent with the typical appearance of a BSNS. However, on resection the tumor was largely composed of a high-grade neoplasm with only focal regions of the low-grade BSNS. This high-grade component demonstrated immunoreactivity for two muscle markers but no longer retained the neuronal differentiation. It also harbored a *PAX3* translocation. While it did not have the *FOXO1* fusion partner, other fusion partners were not covered in the FISH testing and could not be excluded. To the best of our knowledge, this represents the first case of high-grade transformation/dedifferentiation in a BSNS.

Conclusion

Because of the recency of the description of BSNS as a diagnosis, the biologic and clinical behaviors of these lesions have yet to be fully described. While it considered to be a low-grade sarcoma, it is highly possible that high-grade BSNS lesions may have been historically diagnosed as another high-grade sarcoma. This case describes a new category for this malignancy which may influence the diagnostic work-up, extent of surgery, and adjuvant therapies being utilized to treat these lesions.

Conflict of Interest
None declared.

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