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Letter to the editor

Cervical nodal metastasis after malignant conversion of sinonasal inverted papilloma: Report of a rare case and literature review

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ABSTRACT

Malignant conversion of sinonasal inverted papilloma (SNIP) occurs in approximately ten percent of cases. These tumors are classically described as locally destructive, but without metastatic potential. Only four cases of malignant conversion with cervical nodal metastases have been described in the English literature. We present the rare case of a 61-year-old Caucasian male with a nasopharyngeal recurrence of malignant SNIP with cervical and retropharyngeal nodal metastases. The patient underwent endoscopic transpterygoid with nasoseptal flap reconstruction, followed by staged bilateral and retropharyngeal node dissection. Histopathology of the specimens demonstrated poorly differentiated invasive nonkeratinizing squamous cell carcinoma with inverted-type features. Three months after surgery, the patient suffered from C1-C2 fractures consistent with osteoradionecrosis and expired. Although the rate of malignant conversion of SNIP is low, this case highlights the need for aggressive, definitive treatment and surveillance.

Dear Editor,

We recently encountered an unusual case that challenged our traditional understanding of malignant sinonasal inverted papilloma (SNIP) tumor behavior and decided to present it as a case example for discussion.

A 61-year old Caucasian male with a history of a multiply recurrent SNIP with malignant conversion to squamous cell carcinoma (SNIP/SCC) was referred to our office after developing local recurrence and regional metastasis despite multiple resections and adjuvant therapies. The first resection of his tumor occurred ten years ago, with malignant conversion occurring five years later. He subsequently underwent left neck dissection and adjuvant chemoradiation, which was completed in 2015. He again recurred in 2018 at the posterior nasal septum, sphenoid, and frontal sinus, and underwent endoscopic resection demonstrating squamous cell carcinoma in situ with inverted features. Four months postoperatively, he developed a left neck mass concerning for regional metastasis and was referred to our institution. Magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT) demonstrated ^{18}F-fluorodeoxyglucose (FDG)-avid nasopharyngeal recurrence with clival erosion, without intracranial extension (Fig. 1A-B), left cervical node avidity (Fig. 1C), and left retropharyngeal node avidity (Fig. 1D). After multidisciplinary discussion, endoscopic resection was recommended for the nasopharynx, followed by staged bilateral and retropharyngeal neck dissection, and adjuvant therapy as indicated.

The patient underwent endoscopic transpterygoid nasopharyngectomy with resection of the clivus and Eustachian tube with nasoseptal flap reconstruction. Histopathology of the main specimen demonstrated poorly differentiated invasive nonkeratinizing squamous cell carcinoma with inverted-type features (Fig. 2A). P16 immunostaining and Epstein-Barr virus (EBV) in-situ hybridization were both negative. The patient was taken to the operating room again three weeks later for bilateral modified radical neck dissections and left retropharyngeal nodal dissection. Pathology from the nodal specimens demonstrated metastatic nonkeratinizing basaloid squamous cell carcinoma with inverted-type papillomatous architectural features consistent with the resected primary specimen (Fig. 2B). Due to previous radiation fields, only postoperative systemic therapy was recommended, but was delayed due to significant postoperative dysphagia necessitating gastrostomy placement. Three months after surgery, the patient suffered from C1-C2 fractures consistent with osteoradionecrosis versus recurrence and expired at home.

Discussion

SNIP's are benign, locally destructive tumors that can develop malignant conversion in up to ten percent of cases [1–3]. Currently, only four cases of SNIP/SCC with cervical nodal metastasis are reported in the English-language literature. Mazlina et al. first described a case of metastatic SNIP/SCC from the middle ear in 2006, while Mathew et al. described the first case of metastatic SNIP/SCC of sinonasal origin [4,5]. In 2015, Lewis et al. reported an indolent case of human papilloma virus (HPV)-negative SNIP/SCC with metastasis to cervical lymph nodes [6]. Also in 2015, Zhang et al. described SNIP/SCC presenting as a cancer of unknown primary in the neck [7]. Our patient's case further emphasizes the unusual potential for regional metastasis in SNIP/SCC tumors. Aggressive management was pursued for our patient given his tumor's propensity for local recurrence and metastasis.

Outcomes literature for SNIP/SCC remains sparse. Recent small retrospective series have shown that high-grade pathology, advanced T-stage, single-modality therapy, age, metachronous tumors, and orbit and cranial base invasion have been identified as poor prognostic indicators [1,2,8]. In a study of 32 patients with SNIP/SCC by Yu et al, three patients developed distant metastases to lung and brain but no cervical nodal metastases [8]. In another analysis of 87 patients with SNIP/SCC by Liang et al, five patients (~6%) were reported as having cervical nodal metastases, and 27 eventually developed distant

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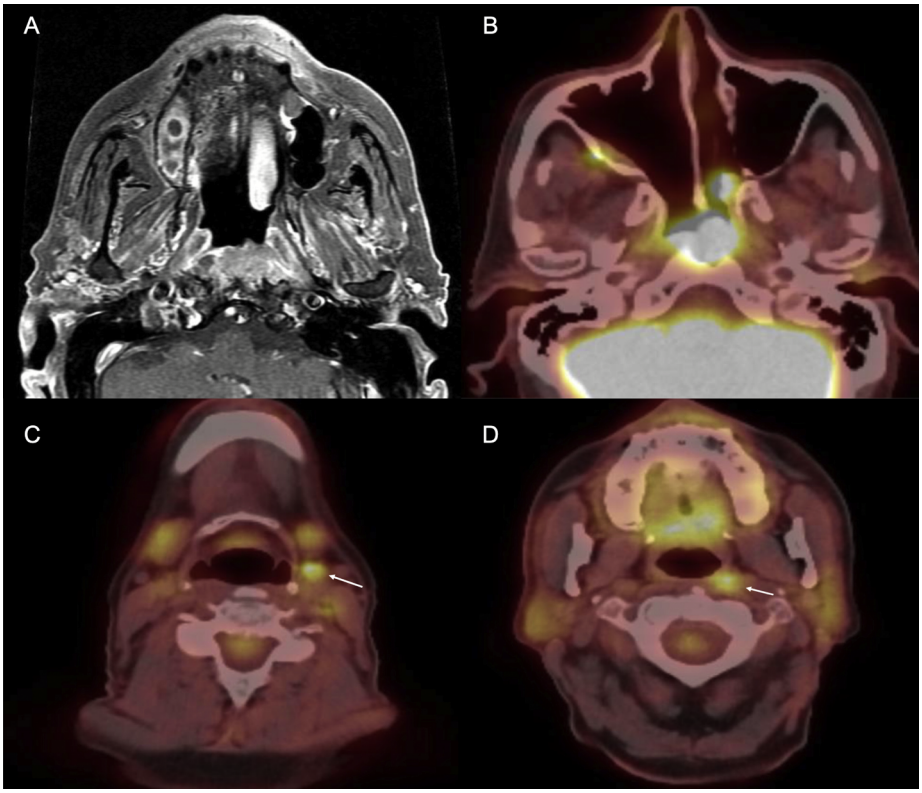

Fig. 1. Findings on Imaging. Contrasted axial T1 MRI (A) and axial PET/CT (B) demonstrating FDG-avid nasopharyngeal primary lesion with erosion into the clivus without intracranial extent. FDG-avid cervical (C, arrow) and retropharyngeal (D, arrow) demonstrating nodal metastatic disease.

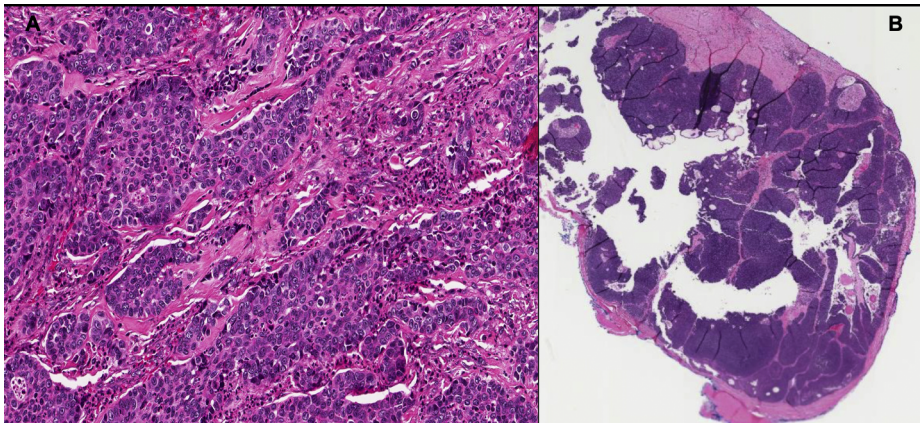

Fig. 2. A. Histopathologic Images. Hematoxylin & eosin (H&E) stain of primary nasopharyngectomy specimen demonstrating poorly differentiated invasive squamous cell carcinoma with inverted-type features (A, original magnification 20×), and H&E stain of the left retropharyngeal nodal specimen demonstrates architecture of nonkeratinizing basaloid squamous cell carcinoma with inverted-type features consistent with metastasis (B, original magnification 0.8×).

metastases, while 2 patients developed neck recurrence [2]. The 5-year overall survival (OS) in these two cohorts was 72.5% and 39.3%, respectively. A recent study by Lobo et al. comparing 88 patients sinonasal SCC without related SNIP to 29 patients with SNIP/SCC demonstrated no cases of cervical nodal metastasis in the SNIP/SCC group compared to 18% incidence in the SCC patients without related SNIP [1]. OS averaged 3.4 years for patients with SNIP/SCC. Taken together, these studies portend a relatively poor prognosis for patients with advanced SNIP/SCC and suggest that aggressive management is required in order to achieve disease control.

While various strains of HPV are often implicated in the pathogenesis of benign and malignant papillomatous lesions of the upper aerodigestive tract, the role of the virus in malignant conversion of SNIP is less clear [3,6]. Previous studies have shown, on-average, 25% of SNIP lesions to be HPV-positive and have suggested the virus plays a tumorigenic role in this subset of lesions [3]. A recent meta-analysis reported a 33.3% (347/1041) and 26.2% (70/322) incidence of HPV-positivity in SNIP's and SNIP/SCC's, respectively [9]. Another separate meta-analysis by Zhao et al. demonstrated HPV-18 to have a statistically significant association with malignant conversion of SNIP's [10]. EBV has also been implicated in the pathogenesis and regional metastasis of nasopharyngeal and sinonasal carcinomas but not in the malignant conversion of SNIP [11,12]. In our patient's malignancy, neither HPV nor EBV were found to play a role.

In Zhang et al.'s report of metastatic SNIP/SCC presenting as a cancer of unknown primary, they noted the inability of PET/CT to initially distinguish the primary tumor in their patient [7]. In their patient's case, the SUV_{max} of the bilateral maxillary sinuses was 4.02 with no evident primary lesion on imaging. A mass was noted in the right nasal cavity, but biopsy only revealed chronic inflammation, and the primary lesion was not identified prior to the patient receiving definitive neck irradiation. He subsequently recurred, underwent local salvage surgery, and later succumbed to his disease after suffering brain metastases. As the authors note, PET/CT remains an imperfect tool for

identifying primary lesions in cancers of unknown primary, and it cannot be used to distinguish benign or malignant lesions. Rather, its role is adjunctive in clarifying the clinical picture of the individual patient. During workup of our patient, we found PET/CT to be a useful adjunct in identifying lesions at both the primary site and the regional nodes, consistent with a malignant process with regional metastasis.

In conclusion, our patient's case exemplifies the very rare metastatic potential of SNIP/SCC, as well as the significant challenges in diagnosing, surveilling, and treating multiply recurrent SNIP/SCC's.

Conflict of interest statement

The authors have no conflicts of interest or financial disclosures to declare.

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