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CASE REPORTS

Lobular to Lobule: Metastatic Breast Carcinoma to Olfactory Neuroblastoma

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Abstract

Tumor-to-tumor metastasis (TTM) is a rare, but well-described phenomenon occurring in patients with multiple synchronous or metachronous primary malignancies. Olfactory neuroblastoma (ONB) is a rare malignant, neuroectodermal sinonasal tract tumor that occurs within the ethmoid sinus involving the cribriform plate. Very few cases of ONB have been documented to metastasize to other primary malignancies, but the reverse scenario is exceptional. During an evaluation for anosmia, a right nasal polyp was identified on imaging and endoscopy in a 66-year-old woman, with a polypectomy performed. Histologic examination showed classical features of a low-grade olfactory neuroblastoma, but within the tumor were isolated epithelioid cells which were strongly pancytokeratin immunoreactive. Review of the clinical history revealed lobular breast carcinoma treated 10 years earlier. Further evaluation with immunohistochemistry showed strong and diffuse nuclear estrogen and progesterone receptor reactivity, along with GATA3. These results confirmed TTM of an invasive lobular breast carcinoma to ONB. By employing a limited immunohistochemistry panel for all small round blue cell tumors that includes pancytokeratin, p40, S100 protein, SOX10, synaptophysin, desmin, CD99, and CD45, one is able to more accurately diagnose the classical tumor types, while also showing potentially unusual tumor features or exceptionally rare events like metastatic lobular breast carcinoma to ONB.

Keywords Olfactory neuroblastoma · Metastases · Ethmoid sinus · Tumor-to-tumor metastasis · Lobular breast carcinoma · Immunohistochemistry

Introduction

Tumor-to-tumor metastasis (TTM) is a rare, but well-described phenomenon in patients with multiple synchronous or metachronous primary malignancies. Previous literature has reported that renal cell carcinoma and meningioma are the most common recipients of TTM, whereas lung and breast carcinomas are the most prevalent tumor donors [1–3].

Metastases to the head and neck are generally infrequent with the incidence of metastases to the nasal cavity and paranasal sinuses specifically being rarer still when compared to other head and neck regions [4]. The most common tumor primary sites to disseminate to this region are kidney (40%), lung (9%), breast (8%), thyroid gland (8%), and prostate (7%). Olfactory neuroblastoma (ONB) (formerly esthesioneuroblastoma), is a malignant, neuroectodermal sinonasal tract (SNT) tumor accounting for 2–3% of SNT malignancies [5–7]. Whereas there are a few case reports of ONB metastasizing to other primary malignancies, the reverse scenario of a malignant tumor metastasizing to an ONB is vanishingly uncommon. It is important to recognize that ONB may have isolated foci of divergent epithelial, rhabdomyoblastic, or melanocytic differentiation recognized histologically and confirmed immunophenotypically, but these findings are not classified as a TTM event [5, 8–14]. We herein report a case of invasive lobular breast carcinoma metastasizing to an ONB. Additionally, we discuss the diagnostic challenges posed by ONBs with unusual morphology

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and posit helpful features in distinguishing TTM involving an ONB from other sinonasal neuroendocrine tumors and an ONB with divergent differentiation.

Case Report

Clinical Presentation

A 66-year old woman was referred to the ear, nose, and throat department due to a 6-month history of right nasal obstruction and sporadic clear nasal discharge. She had a nine-year history of decreased sense of smell without any associated facial pain or epistaxis. Imaging studies showed sinonasal polyps. Treatment with intra-nasal steroid drops yielded little symptomatic improvement.

Her past medical history was significant for bilateral mastectomy and adjuvant chemotherapy for breast cancer 10 years prior to presentation [15]. Pathology showed invasive breast carcinoma of no special type (ductal) grade 2 in the left breast while the right breast contained an invasive lobular carcinoma grade 2 (Fig. 1). Both tumors were estrogen and progesterone receptor positive. She had been managed with Tamoxifen therapy for five years. Seven years after her initial diagnosis, she developed liver and bone metastases, which were managed with capecitabine and bisphosphonate therapy. Her disease remained unchanged for the ensuing three years. During evaluation for the nasal obstruction by nasoendoscopy, a 2.5 cm erythematous polyp was identified in the right nasal cavity. A computed tomography (CT) scan of the sinuses was performed and confirmed a polyp extending from high in the right nasal cavity and filling the nasal vault (Fig. 2). She underwent endoscopic right nasal polypectomy. Postoperatively, her nasal obstruction and anosmia had resolved and repeat CT and magnetic resonance imaging (MRI) of the sinuses showed no residual disease. She was subsequently restarted on capecitabine and remains under regular oncologic follow-up.

Pathology

The excised polypectomy specimen consisted of a 25 mm polyp. Histologically, the polypectomy showed sheets and nests of cells arranged in a lobular architecture, separated by a delicate fibrovascular stroma (Fig. 3). The tumor cells were small, showing a high nuclear to cytoplasmic ratio. The cells showed a syncytial appearance with scant, wispy cytoplasm surrounding round to oval nuclei with delicate, granular to salt-and-pepper nuclear chromatin distribution. Nucleoli were inconspicuous. Tumor necrosis, increased mitoses, and pleomorphism was absent, although 5 mitoses/2 mm^2 were seen. Within this background, clustered in several of the tumor lobules, were isolated to focally aggregated, epithelioid cells (Fig. 3). They were preferentially in the lobules, but some of the cells were within vascular channels. This second population of

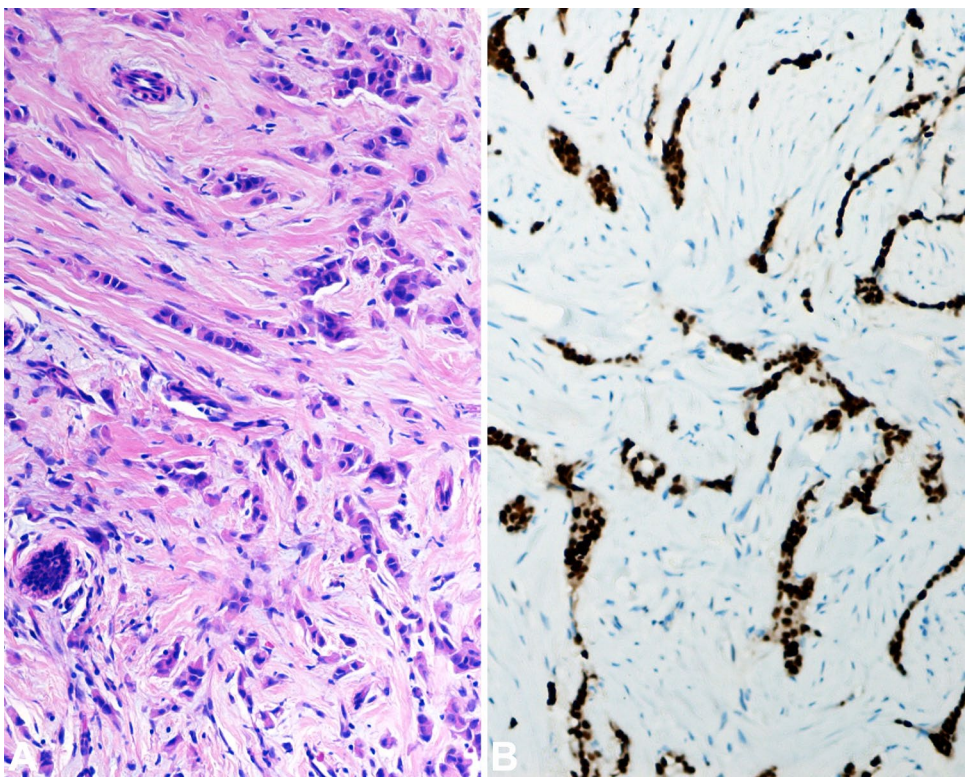

Fig. 1 **a** Infiltrating lobular breast carcinoma showing a low nuclear grade, with small mucinous cytoplasmic vacuoles. **b** The neoplastic cells show a strong and diffuse nuclear reactivity for estrogen receptor by immunohistochemistry

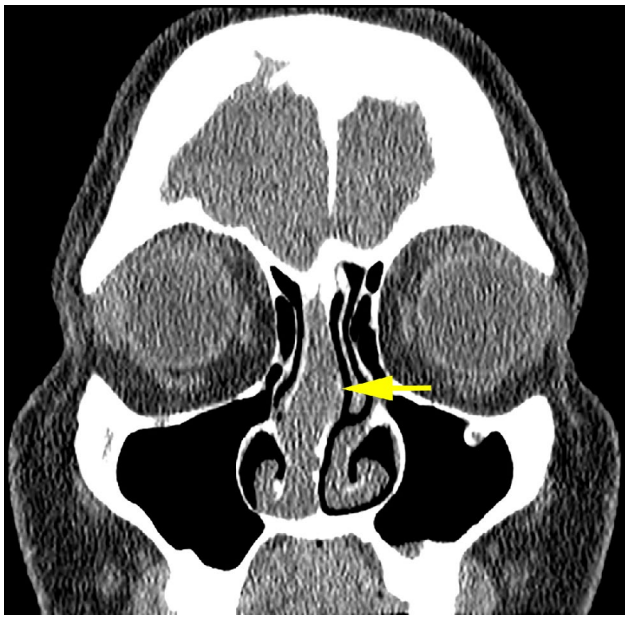

Fig. 2 Computed tomography demonstrates a mass filling the right nasal cavity (yellow arrow) with extension up to the ethmoid sinus

cells was epithelial in appearance, showing eosinophilic cytoplasm with eccentric nuclei that were more hyperchromatic with visible nucleoli. Small cytoplasmic vacuoles were noted, pushing the nucleus to the side. There was no pigmentation, no keratinization, and no well-developed intercellular borders/bridges.

An immunohistochemistry panel was performed (CAM5.2, p63, S100 protein, synaptophysin, CD99, desmin, ß-catenin), which showed two distinct populations. The *dominant* population–olfactory neuroblastoma cells–was highlighted with synaptophysin, bounded by a very delicate sustentacular S100 protein immunoreactivity (Fig. 4), while the *minor* population was strongly positive with CAM5.2 (Fig. 4). The remaining initial immunohistochemistry studies were negative. Additional immunohistochemical studies were performed, based on the dual nature of the cells and the known clinical history of invasive lobular breast carcinoma, with the second, *minor* population highlighted by CK7, GATA3, and estrogen and progesterone receptors. The lobular breast carcinoma phenotype was confirmed by negative staining for e-cadherin and a granular cytoplasmic P120 catenin, while CK5/6, TTF1, CK20, and Her-2/neu were negative (positive and negative controls were appropriate). These findings supported a metastatic breast carcinoma, and a lobular carcinoma based on the morphologic appearance. Overall, these features represent tumor-to-tumor metastasis of a lobular breast carcinoma to an olfactory neuroblastoma.

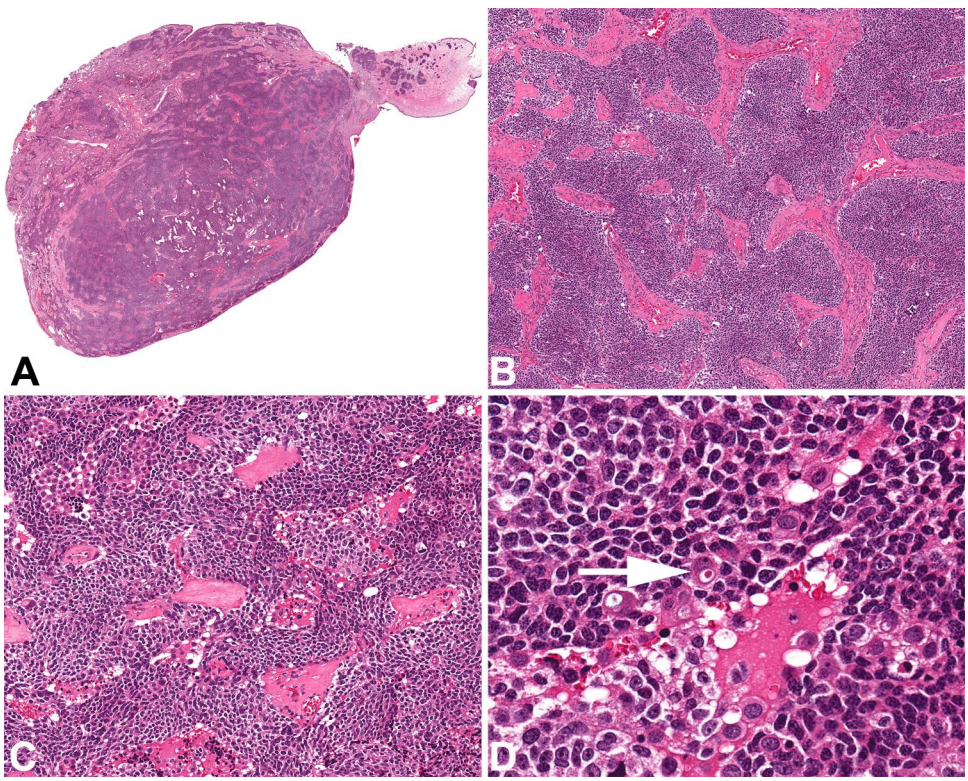

Fig. 3 **a** A polyp filled with a highly cellular neoplastic proliferation showing a lobular architecture. **b** A richly vascularized stroma divides the neoplastic cells into lobules. There is a small round blue cell appearance to the proliferation. **c**, Olfactory neuroblastoma is composed of small cells arranged in a sheet-like to lobular distribution with scant cytoplasm. However, numerous epithelioid cells ae noted within the lobules as well as in the vascular spaces. **d**, Olfactory neuroblastoma is noted in the background, with dense, hyperchromatic chromatin distribution. Isolated cells and small clusters of epithelial cells with vacuoles (white arrow), are the second population of metastatic lobular of the breast carcinoma

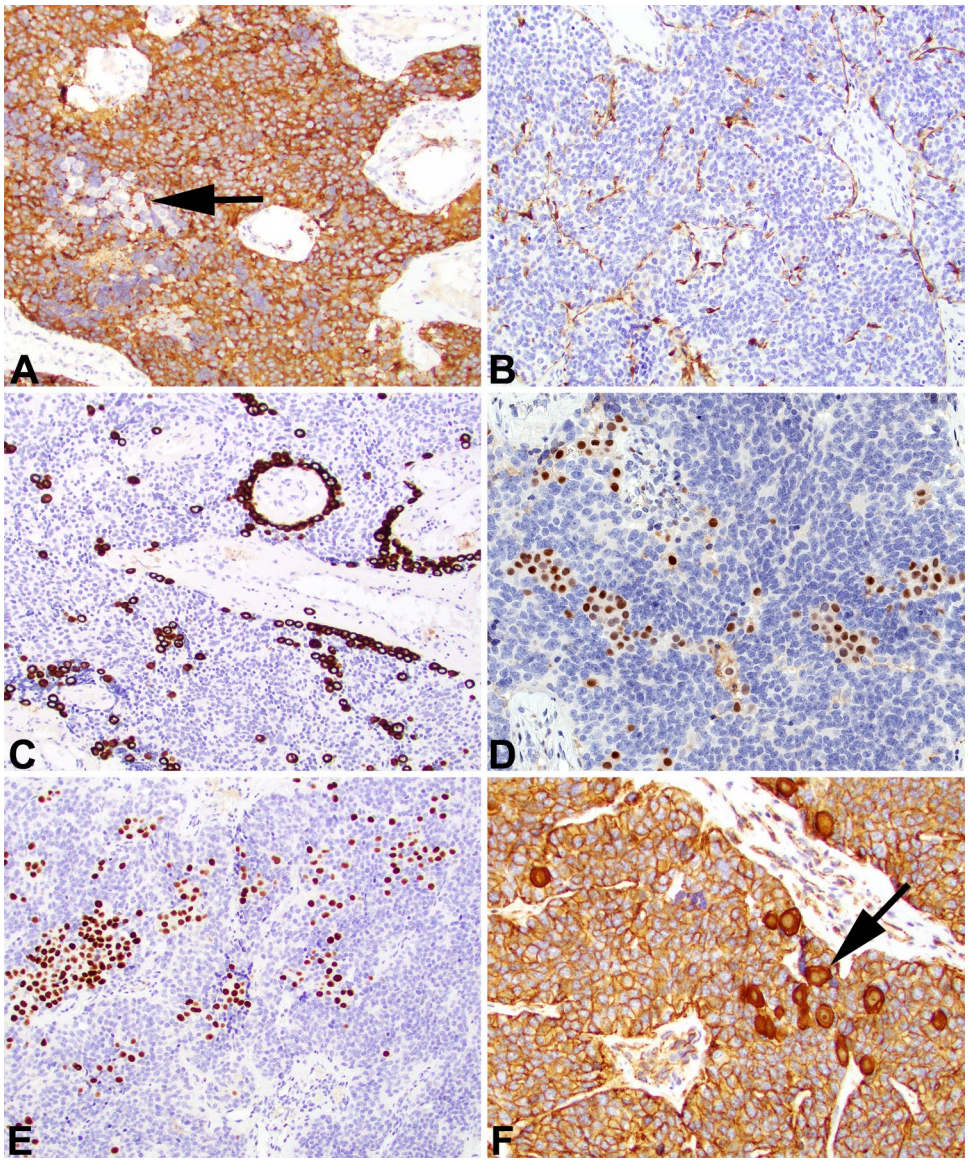

Fig. 4 A number of immunohistochemistry studies highlight the two components of the tumor to tumor metastasis. **a** Synaptophysin shows a strong and diffuse reaction with the neuroblastoma cells, while the negative cells are the lobular breast carcinoma (black arrow). **b**, S100 protein shows a delicate, sustentacular supporting framework reactivity. **c**, CAM5.2 strongly highlights the metastatic breast carcinoma cells and clusters, specifically aggregated around vessels. **d**, Estrogen receptor protein is strongly and diffusely immunoreactive in the nuclei of the metastatic breast carcinoma cells, which are also highlighted by **e**, GATA3 and **f**, show a strong cytoplasmic granular reactivity with p120 catenin

Discussion

The rare phenomenon of a tumor metastasizing to another tumor, clinically termed tumor-to-tumor metastasis (TTM), was first reported in the English literature by Berent in 1902 with only an additional couple hundred cases reported subsequently [2, 3, 16]. Campbell, et al., [17] described specific criteria in 1968 that are required to make a true diagnosis of TTM: the patient must have two or more different tumors, with the recipient tumor being a true benign or malignant neoplasm [1]; the metastatic neoplasm must be a true metastasis, without contiguous growth between the tumors; the metastatic tumor must be morphologically and immunophenotypically compatible with the primary neoplasm; exclusion of cases where tumors metastasize to the lymph node system where another metastatic tumor is also present [17].

Metastases to the head and neck are generally infrequent with the prevalence of metastases to the nasal cavity and paranasal sinuses specifically being rarer still when compared to other head and neck regions [4]. Most of these cases are seen with disseminated disease and can occur at any age. The most common tumor sites to disseminate to this region are the kidney (40%), lung (9%), breast (8–20%), thyroid gland (8%), and prostate (7%), with obvious sex differences. It is not uncommon for these metastases (up to 35% of cases) to be the first manifestation of an otherwise clinically occult carcinoma.

Diagnosing lesions in the sinonasal tract can be challenging as the differential diagnosis of malignant tumors in this region can be extensive [5]. Squamous cell carcinoma is by far the most common malignancy, representing 55% of SNT malignancies, with other epithelial, mesenchymal,

melanocytic, lymphoid, and neuroectodermal tumors making up the rest [5, 6].

Unique sinonasal tract tumors include olfactory neuroblastoma, sinonasal undifferentiated carcinoma, and ectopic pituitary neuroendocrine tumors (PitNET), all three of which show neuroendocrine differentiation histologically and by immunohistochemistry, with primary neuroendocrine carcinoma included in the neuroendocrine neoplasm category. Immunohistochemical plasticity and lineage infidelity can be seen with extranodal NK/T-cell lymphoma, nasal type, rhabdomyosarcoma, and mucosal melanoma, which contribute to diagnostic difficulties [18–24].

Olfactory neuroblastoma (ONB) is a malignant neuroectodermal neoplasm that belongs to a group of primary sinonasal neuroendocrine tumors, with high grade tumors frequently showing both histologic and immunohistochemical overlap with other tumors in the neuroendocrine category. These uncommon entities are distinguished by site of origin, cell type, immunohistochemical findings, and biologic behavior. Without creating a taxonomic quagmire, it is generally accepted that low grade (grades 1 and 2) ONB can be easily separated from other tumors in the differential diagnosis. The lobular architecture is one of the persistent findings in the tumor, and hence the alliteration of lobular carcinoma metastasis to a lobule of ONB used in the title. Using a pertinent panel approach, that includes pancytokeratin, p40 and/or p63, S100 protein, SOX10, synaptophysin, desmin, CD99, and CD45, one is able to reach a reasonable algorithmic interpretation that creates branches that direct additional studies to further hone the diagnosis. Thus, in a unique case such as this, if the panel were performed, the synaptophysin and S100 protein reactivity supports the ONB diagnosis, while the strong and diffuse, but isolated pancytokeratin (a CAM5.2 was performed, which is immunophenotypically equivalent) positive cells led to the interpretation of a second population being present. Additional investigation of that population resulted in the correct diagnosis.

Rare cases of ONB with divergent differentiation show focal populations of cells with distinct morphologic characteristics, including melanocytic, myogenic, neural, or epithelial qualities (i.e. gland formation or squamous morules) [5–7]. However, these specific changes have been described as focal findings within portions of an otherwise classical or characteristic ONB. Faragalla, et al. postulated these focal divergent histologic characteristics may only be seen following chemoradiation or in distant metastases where the divergent cell types are similar to the local recipient tissue [6]. Three reported cases of coexistence between ONB and non-neuroendocrine tumors have been described [5, 25, 26]. However, only one of these cases described carcinomatous involvement, but was described in 1984 where the analysis did not include many of the current immunohistochemical markers performed to distinguish ONB from similar sinonasal tumors [25].

There is a recently published case of a high grade ONB that was intimately associated with a non-neuroendocrine, cytokeratin and EMA-reactive population thought to represent "olfactory carcinoma" [5]. While ONB may occasionally demonstrate focal or rare keratin-reactive cells, this reported case had a larger proportion of cell nests reactive for epithelial markers. These same islands of cells were reported to be negative for neuroendocrine immunohistochemical markers. Further, the overlying mucosa was described as showing severe epithelial dysplasia or carcinoma-in-situ. Alas, there is no documentation of additional imaging to exclude an occult primary that may support TTM.

The surgical pathology of the case presented here is unique in that it displayed many of the classic histologic and immunohistochemical features of ONB, while it also displayed a distinct second population of cytokeratin, ER, PR, GATA3, and p120 catenin (granular cytoplasmic) immunoreactive single and small groups of cells throughout the ONB, diagnostic of TTM by a lobular breast carcinoma to ONB.

The most common mode of spread of ONB is by direct extension with metastatic spread being much less common [27]. There are rare cases in the literature describing TTM involving ONB with a case of ONB metastasizing to a radiation-induced meningioma within four years of undergoing a craniofacial resection and post-operative radiotherapy for ONB [28]. Further, ONB has been documented to metastasize to the breast, but not to a breast neoplasm [29]. Breast carcinoma (BC) is the most common malignancy in women and is responsible for a large proportion of cancer deaths [30]. BC is among the most common tumors to metastasize to the head and neck, constituting about 20% of all metastases to this region [30, 31]. Even so, the absolute frequency of BC metastasizing to the head and neck is low given metastases to the head in neck is generally uncommon and can pose significant diagnostic difficulty [30, 31]. The large variability in lapsed time between the original diagnosis and discovery of metastatic disease contributes to the challenging nature of this diagnosis for both clinicians and pathologists alike. Additionally, BC patients with metastatic spread to the head and neck can have unusual presentations that further complicate making an accurate diagnosis [30]. However, there should be increased awareness of metastasis when BC patients experience headache, nasal obstruction, cranial nerve palsies without a mass lesion, or other sinus-related symptoms. The 5-year survival rate decreases significantly when there is locally advanced disease with regional lymph node metastases (85%) versus documentation of distant metastatic spread (25%) [30].

Despite the rarity of tumor-to-tumor metastases in general, and even more so for an olfactory neuroblastoma,

special attention should be paid to the patient's oncologic history to ensure an accurate diagnosis is rendered. A pathologist's index of suspicion should be high for TTM if tumors of the sinonasal tract have unusual morphology or when multiple malignant cell populations can be identified.

In this case, the patient has done well postoperatively, with resolution of her nasal obstruction and anosmia. Repeat CT and MRI of the sinuses have shown no residual disease as she undergoes regular oncologic follow-up.

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Compliance with Ethical Standards

Conflict of interest The authors declare they have no conflict of interest as it relates to this research project.

Ethical approval All procedures performed in this case report involving human participants were in accordance with the ethical standards of the institutional review board (IRB #5968), which did not require informed consent.

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