Sinonasal epithelial-myoepithelial carcinoma: Report of a novel subsite and review of the literature

Theodore A. Schuman, M.D.,[1] Adam J. Kimple, M.D., Ph.D.,[2] Claire H. Edgerly, M.D.,[3] Charles S. Ebert Jr, M.D., M.P.H.,[2] Adam M. Zanation, M.D.,[2] and Brian D. Thorp, M.D.[2]

ABSTRACT

Background: *Epithelial-myoepithelial carcinoma (EMC) is a rare tumor of the major and minor salivary glands. Sinonasal EMC is extremely uncommon and hitherto not described within the frontal or ethmoid sinuses.*

Objective: *To present a novel sinonasal subsite and review the literature regarding sinonasal EMC.*

Methods: *A case of frontoethmoidal EMC was presented. A medical literature data base was queried from January 1, 1950, to August 8, 2017, for all reports of sinonasal EMC.*

Results: *A 69-year-old man underwent combined open and endoscopic craniofacial resection of a right frontoethmoidal EMC, a previously undescribed primary location for this tumor. A comprehensive review of the literature revealed 13 additional cases of sinonasal EMC.*

Conclusion: *EMC is an uncommon neoplasm typically found in the major salivary glands; occurrence in the nose or paranasal sinuses is extremely rare. EMC often follows an indolent clinical course, although, in a minority of cases, particularly in large tumors with nuclear atypia, more aggressive behavior may be observed.*

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Epithelial-myoepithelial carcinoma (EMC) is an extremely rare neoplasm that typically occurs in the major salivary glands, predominantly the parotid,[1] although it has also been reported in the external auditory canal,[2,3] lacrimal gland,[4–6] nasopharynx,[7,8] palate,[9,10] floor of the mouth,[11] buccal mucosa,[12] base of the tongue,[13,14] larynx,[15] subglottis,[16,17] hypopharynx,[18] trachea,[19] lung,[20–23] liver,[24] and Bartholin gland.[25] EMC was first described in 1972[26] and is histologically a biphasic tumor that consists of clear-staining myoepithelial cells surrounding epithelial-lined ductal cells.[27]

EMC of the major salivary glands demonstrates a female preponderance and commonly follows an indolent clinical course. In the largest cohort study to date, which consisted of 246 patients with salivary EMC, Vazquez *et al.*[1] reported an overall 5-year disease-specific survival of 91.3%, with distant metastasis observed in only 4.5% of patients. A tumor size of >4 cm and high-grade histology (6.5% of patients) were found to be associated with increased mortality. Treatment consisted of surgery, with adjuvant radiation administered to 39% of patients, although no survival benefit was found with the addition of radiation therapy.[1]

Sinonasal EMC is exceedingly rare, with a total of 13 individual cases described within the English language literature (Table 1). Within the paranasal sinuses, this neoplasm was previously reported only in the maxillary region.[28–31] The current study presented a novel case of EMC that originated in the anterior ethmoid sinus and extended into the frontal recess, followed by a review of the available literature regarding the diagnosis and management of sinonasal EMC.

CASE REPORT

A 69-year-old man reported progressive hyposmia and self-limiting right-sided epistaxis of 2 years' duration. The patient had been treated with broad-spectrum antibiotics on multiple occasions for presumed recurrent acute sinusitis. He subsequently was evaluated by an otolaryngologist at a different facility who obtained preoperative computed tomography and magnetic resonance imaging, which revealed a 3.6-cm enhancing mass of the right anterior ethmoid region with associated obstruction of the right frontal sinus (Fig. 1). The patient subsequently underwent septo-

From the [1]Department of Otolaryngology—Head and Neck Surgery, Virginia Commonwealth University School of Medicine, Richmond, Virginia, [2]Department of Otolaryngology—Head and Neck Surgery, University of North Carolina School of Medicine, Chapel Hill, North Carolina, and [3]Department of Pathology and Laboratory Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina

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Address correspondence to Brian D. Thorp, M.D., Department of Otolaryngology—Head and Neck Surgery, University of North Carolina School of Medicine, 170 Manning Drive CB 7070, Chapel Hill, NC 27599

E-mail address: brian_thorp@med.unc.edu

Table 1 **Published cases of epithelial-myoepithelial carcinoma that occurred within the nose and paranasal sinuses**

Study	Age, y/ Sex	Presentation	Site of Origin	Primary Tumor	Metastasis	Surgical Approach	Adjuvant Radiation	Outcome
Current study, 2018	69/male	Hyposmia, epistaxis for 2 y	Anterior ethmoid	3.6 cm, extension to frontal sinus	None	Open and endoscopic craniofacial resection	66 Gy to resection site and bilateral cervical lymph nodes	No recurrence at 8 mo
Amita *et al.*,[36] 2016	60/female	Nasal obstruction, epistaxis, facial swelling, vision change, headache for 3 mo	Nasal cavity, unspecified	Unspecified	Distant (bilateral lung)	None	Not available	Distant metastasis at initial diagnosis; referred for radiotherapy and lost to follow-up
Flam *et al.*,[37] 2015	63/male	Epiphora for 2 y, epistaxis for 1 y	Nasal cavity lateral to inferior turbinate	1.6 cm, obstruction of nasolacrimal duct	None	Endoscopic medial maxillectomy	No	No recurrence at 12 mo
Patra *et al.*,[29] 2012	50/male	Cheek swelling for 7 y, nasal obstruction and epistaxis for 3 mo	Maxillary sinus	8 cm, erosion into the orbit, soft tissues of the face, and the oral cavity	Contralateral cervical lymph node (4 mo after initial resection)	Lateral rhinotomy and/or sublabial approach for primary tumor; selective neck dissection for recurrence in contralateral neck	30 Gy after initial resection; unspecified dose to the neck after recurrence	Initial recurrence at 4 mo, treated with neck dissection and adjuvant radiotherapy; no further recurrence at 24 mo
Chung *et al.*,[38] 2013	48/female	Nasal obstruction for "several months"	Nasal cavity, unspecified	5 cm, extension to nasopharynx, hard palate, alveolus	None	Unspecified	Unspecified	Unspecified
Park *et al.*,[32] 2011	36/female	Unspecified	Inferior turbinate	0.5 cm	Distant (bone)	Endoscopic	No	Recurrence at 15 mo in contralateral nasal cavity
						Medial maxillectomy for recurrence in contralateral inferior turbinate	60 Gy after recurrence	Distant metastasis at 22 mo
Kuran *et al.*,[30] 2008	54/female	Facial swelling for 6 mo	Maxillary sinus (bilateral)	6.5 and 4.5 cm, extension to hard palate and nasal cavity	None	Partial maxillectomy	No	No recurrence at 30 mo
Yamanegi *et al.*,[39] 2008	70/female	Epistaxis for 3 mo	Inferior turbinate	3.6 cm, confined to nasal cavity	None	Unspecified	No	No recurrence at 12 mo
Pradhan *et al.*,[40] 2007*	29/male	Facial swelling, epistaxis, and nasal obstruction for 6 mo	Unknown	Recurrent tumor of nasal cavity that extended to maxillary sinus	None	Lateral rhinotomy	No	Unspecified
Lee *et al.*,[41] 2000	22/male	Nasal obstruction for 1 y	Inferior turbinate	3 cm, extension to maxillary sinus and soft palate	None	Partial maxillectomy	55 Gy	No recurrence at 40 mo
Jin *et al.*,[42] 1999	61/female	Nasal obstruction and epistaxis for 2 mo	Posterior nasal cavity	4 cm, extension to nasopharynx	None	Unspecified	No	No recurrence at 20 mo

Continued

Table 1 **Continued**

Study	Age, y/ Sex	Presentation	Site of Origin	Primary Tumor	Metastasis	Surgical Approach	Adjuvant Radiation	Outcome
Sunami *et al.*,[28] 1999	65/female	Nasal obstruction for 1 y	Maxillary sinus	7 cm, erosion into hard palate and nasal cavity	None	Unspecified	No	No recurrence at 24 mo
Harada *et al.*,[43] 1996	56/male	Epistaxis for 2 y, nasal obstruction for "several months"	Nasal septum	Unspecified size, no extension or bony erosion	None	Endoscopic	No	No recurrence at 7 mo
Fonseca *et al.*,[31] 1993	74/female	Unspecified	Maxillary sinus	Unspecified	None	Unspecified	Unspecified	Died of locally recurrent disease at 252 mo

**A sinonasal mass had been excised 18 mo before presentation, with no other history available.*

plasty and bilateral functional endoscopic sinus surgery by the outside surgeon, with subtotal resection of the noted right frontoethmoidal mass. The final pathology report was consistent with EMC (Fig. 2).

After this initial procedure, the patient was referred to the multidisciplinary skull base program at the University of North Carolina at Chapel Hill for further management of residual tumor. He underwent combined open and endoscopic craniofacial resection with pericranial flap reconstruction of the anterior skull base. The patient was discharged on postoperative day 7 after removal of nasal packing. He recovered well from the procedure, with no evidence of neurologic complication or cerebrospinal fluid leak. The final pathologic examination showed residual EMC of the right anterior septum and frontal sinus with negative margins. Consensus was reached at the multidisciplinary head and neck tumor board to treat with adjuvant radiation (64.8 Gy) to the tumor site and ipsilateral neck beginning 6 weeks after surgery. The patient currently had no evidence of residual or recurrent disease 8 months after completion of radiotherapy.

METHODS

Clinical data were reviewed after obtaining approval from the institutional review board of the University of North Carolina at Chapel Hill. Surgical specimens underwent standard hematoxylin and eosin staining. Immunohistochemical studies were performed on tissue sections from the primary specimen with antibodies against smooth-muscle actin and pan-cytokeratin (AE1/AE3). Brown staining within a blue background was interpreted as a positive result.

A comprehensive literature review of the MEDLINE data base from January 1, 1950, to August 8, 2017, was performed by using combinations of the search terms "epithelial," "myoepithelial," "epithelial-myoepithelial," "paranasal sinus," "sinus," "nasal," and "nose." Reference sections of identified articles were searched for additional relevant articles. Only those articles published in English were included in this review.

RESULTS

Thirteen relevant English-language case reports[28–32,36–43] were identified (Table 1) for a total of 14 patients with sinonasal EMC, including the current study patient. An additional article reported a heterogeneous series of 61 EMC tumors, including 6 that occurred within the "sinonasal mucoserous glands."[44] Unfortunately, no specific information regarding the sinonasal subsite, pathology, or outcome was provided for this subgroup, and, therefore, these patients were not included in the current review. Of the 14 total patients with sinonasal EMC, 8 (57.1%) were women, with an average age of 54.1 ± 15.7 years. Presenting symptoms

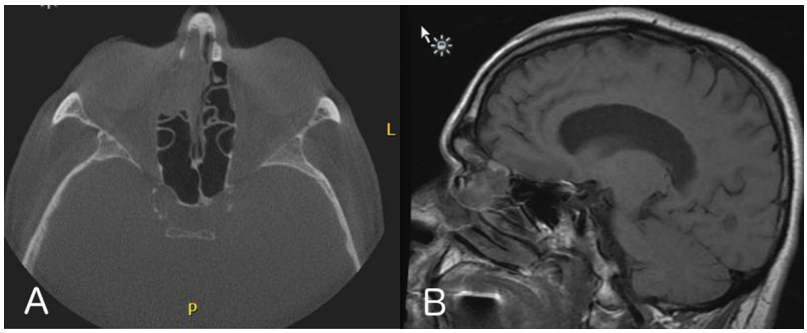

Figure 1. Preoperative imaging. (A) Computed tomography, demonstrating a mass in the right anterior ethmoid sinus, with thinning of the lamina papyracea. (B) Sagittal T1-weighted magnetic resonance image, showing this mass as well as associated frontal sinus obstruction.

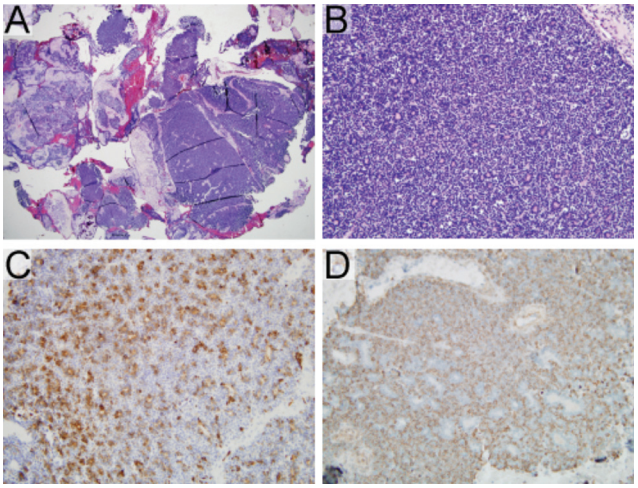

Figure 2. Epithelial-myoepithelial carcinoma. (A) A specimen, demonstrating a densely cellular, multinodular lesion amid background salivary gland tissue (hematoxylin and eosin, original magnification ×20). (B) A specimen, demonstrating small ductal structures within the lesion (hematoxylin and eosin, original magnification ×200). The inner layers of cells are columnar, with granular eosinophilic cytoplasm; surrounding these are layers of cells with indistinct borders, vesicular nuclei, and clear-cell changes in a subset. There is little cytologic atypia or appreciable mitotic activity in either population. (C) Epithelial inner lining cells (pan-cytokeratin immunostain, original magnification ×200). (D) A smooth-muscle actin immunostain is positive in the surrounding myoepithelial cells (smooth-muscle actin immunostain, original magnification ×200).

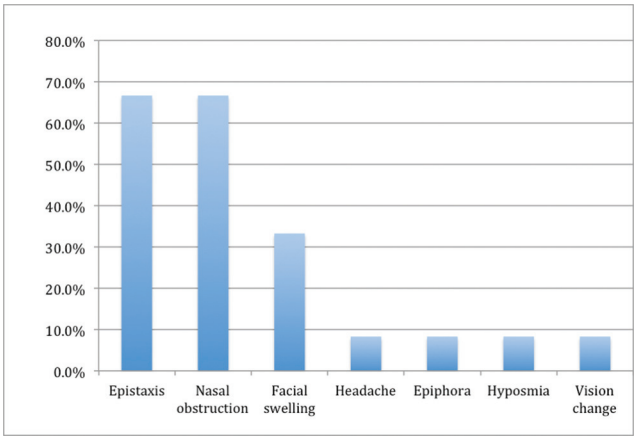

Figure 3. Frequency of presenting symptoms of sinonasal epithelial-myoepithelial carcinoma.

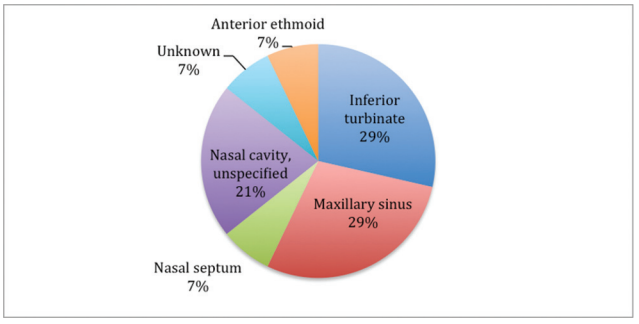

Figure 4. Site of tumor origin.

were available for 12 of 14 patients, with the most common being nasal obstruction and epistaxis. (Fig. 3). Facial swelling, epiphora, hyposmia, headache, and unilateral vision loss were also reported as initial symptoms (Fig. 3). The duration of symptoms before diagnosis ranged from 2 months to 7 years.

The maxillary sinus and the inferior turbinate were the most common location for these neoplasms (Fig. 4). All the lesions were unifocal at the time of presentation, with the exception of one patient who presented with EMC of the bilateral maxillary sinuses.[30] Tumor size ranged from 0.5 to 8.0 cm at the time of surgical resection. Tumor resection was performed through a variety of open and endoscopic approaches, and consisted of at least a partially endoscopic procedure in four of eight patients (50%). Of the patients who underwent primary tumor resection, 3 of 11 (27.3%) received adjuvant radiation. One patient who presented with distant metastasis to the lung was treated with primary radiation therapy alone.

Eleven patients (including the current study patient) had clinical outcome data available; the average follow-up was 41.0 ± 70.6 months. When excluding a dramatic outlier who was reported to have died of locally recurrent disease 252 months after the initial diagnosis, the average follow-up was 19.9 ± 10.4 months. Recurrent disease occurred in 3 of 11 patients (27.3%): 1 patient developed regional metastasis to the

contralateral cervical lymph nodes 4 months after the initial resection[29]; a second patient developed local recurrence in the contralateral nasal cavity at 15 months, followed by distant bony metastases at 22 months[32]; and a third patient was reported to have died from local disease 252 months after diagnosis. The calculated mortality rate was 1 of 11 (9.1%), regional metastasis was 1 of 11 (9.1%), and local recurrence was 2 of 11 (18.2%) at 41.0 ± 70.6 months.

DISCUSSION

The differential diagnosis of sinonasal malignancy is broad; common tumors of the anterior skull base in adults include squamous cell carcinoma, adenocarcinoma, and adenoid cystic carcinoma. A multitude of rarer neoplasms of epithelial, mesenchymal, neuroectodermal, and lymphoid origin may also occur in the ethmoid region, including sinonasal undifferentiated carcinoma, mucosal melanoma, and olfactory neuroblastoma.[33] An uncommon tumor in any location, EMC is especially rare in the nose and paranasal sinuses; the current study described, to our knowledge, the first reported case within the frontal-ethmoid region. A comprehensive English-language literature review identified 13 other patients with EMC of the sinonasal cavity.

A preponderance of cases of EMC arise within the major salivary glands, typically the parotid, and thus the majority of data regarding the natural history of this neoplasm comes from series of patients with salivary tumors.[1] The slight female preponderance (57.1%) and average age (54.1 ± 15.7 years) of the patients with sinonasal EMC were consistent with the largest case series of EMC of the major salivary glands, which also reported a female preponderance (57.3%) and average age of 63.8 ± 15.4 years.[1]

An early case series of EMC of the major and minor salivary glands reported a 50% recurrence and 40% mortality rate for 22 patients with this tumor.[31] More than 2 decades later, a query of the Surveillance, Epidemiology, and End Results data base provided a more optimistic prognosis for salivary EMC; based on 246 patients, the overall survival rates were 91.3% at 60 months, 90.2% at 120 months, and 80.7% at 180 months.[1] Of the 11 patients with sinonasal EMC and adequate follow-up data available, survival at an average of 41.0 ± 70.6 months was 90.9%. The spread to regional lymph node basins and spread to distant metastasis were each seen in 1 of 11 (9.1%) of the study population compared with 22.0 and 4.47% for salivary EMC, respectively.[1] Due to the scarcity of this tumor, the sample size for sinonasal EMC was unavoidably low, which made reliable estimation of mortality difficult. Nevertheless, the concordance seen for survival between populations of salivary and sinonasal EMC supported the conclusion that, in general, EMC is a low-grade neoplasm that follows a relatively indolent clinical course.

In a small proportion of cases, EMC exhibits more aggressive characteristics and decreased overall survival. Vazquez *et al.*[1] identified a tumor size of >4 cm and high-grade histology as independent predictors of increased mortality for salivary EMC at 180 months. Seethala *et al.*[27] reported positive margins, angiolymphatic invasion, necrosis, and myoepithelial anaplasia as predictors of decreased disease-free survival. In their population of 45 patients with follow-up data, 5- and 10-year disease-specific survivals were 93.5 and 81.8%, respectively; only three patients died of disease, but all had positive margins, angiolymphatic invasion, and necrosis on initial resection, with the eventual development of either regional or distant metastases.[27] In an earlier study, of 22 patients with salivary EMC, Fonseca and Soares[31] identified nuclear atypia to be associated with an unfavorable prognosis.

A similar pattern emerges from analysis of sinonasal EMC: most patients have no evidence of recurrent or metastatic disease, yet outliers exist. Park *et al.*[32] reported a 36-year-old woman with a 0.5-cm EMC of the inferior turbinate that recurred in the contralateral nasal cavity at 15 months following initial surgical resection and ultimately resulted in distant metastasis at 22 months following initial surgical resection, despite clear resection margins and adjuvant radiation therapy after excision of the locally recurrent tumor. Although the primary tumor was small, unusually high-grade histology was noted, with significant nuclear atypia, necrosis, and elevated mitotic count.[32] Information regarding histologic grade was not available for other patients with sinonasal EMC, but high-grade lesions reasonably warrant more aggressive management and surveillance.

The treatment approach to sinonasal EMC varied across case reports, with most patients undergoing a combination of open and/or endoscopic resection, with or without adjuvant radiation. The goal of primary surgery for EMC is margin-negative resection, with avoidance of major morbidity. The role for adjuvant radiation in salivary EMC is not established, although it may be recommended for patients with high-risk clinical or histologic features. Postoperative radiotherapy was recommended for the current study patient due to previous incomplete tumor resection by an outside surgeon. The role of chemotherapy in the management of advanced EMC has not been adequately studied, although several case reports have described its effective use for pulmonary metastasis from EMC of the major salivary glands.[34,35] Given the overall rarity of EMC, it is unlikely that adequately powered studies will be

available to assess the comparative value of treatment options, and decisions regarding modalities will need to be made by multidisciplinary tumor boards by taking patient factors and available data into account.

CONCLUSION

EMC of the nose and paranasal sinuses is a very rare tumor, with 14 reported cases in the English language medical literature. To our knowledge, this was the first report of EMC within the frontoethmoidal region. Data are sparse, but, in general, EMC follows an indolent clinical course, although, in a minority of cases, particularly in large tumors with nuclear atypia, more aggressive behavior may be observed. Treatment of nonmetastatic disease consists of surgical excision with clear margins if possible and may include adjuvant radiation.

ETHICAL APPROVAL

This study was approved by the IRB at the University of North Carolina at Chapel Hill.

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies with human or animal subjects.

STATEMENT OF INFORMED CONSENT

There are no human subjects in this article and informed consent is not applicable.

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