Carcinoma ex Pleomorphic Adenoma of the Nasal Cavity

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Abstract

Background Carcinoma ex pleomorphic adenoma (CXPA) is a malignant epithelial neoplasm arising in a benign mixed tumor (i.e., pleomorphic adenoma or PA); it accounts for approximately 3–4% of all salivary gland neoplasms. CXPA is exceedingly rare in the nasal cavity, with only three cases previously documented.

Methods We report two cases of women presenting with masses of the nasal cavity. The tumors were resected and evaluated grossly and by routine microscopy.

Results Both patients presented with nasal obstruction, and one patient reported epistaxis. Grossly, the tumors were 2.5 and 3 cm in greatest dimension, respectively. In each case, microscopic examination of the tumor revealed an infiltrating carcinoma arising in association with foci of benign PA. The carcinoma types were adenoid cystic carcinoma and high grade adenocarcinoma, not otherwise specified. Both cases were widely (i.e., >1.5 mm) invasive

beyond the preexisting PA. The findings were diagnostic of CXPA.

Conclusions Carcinomatous transformation of a PA in the nasal cavity is extremely rare, but does occur. Accordingly, PAs of this site should be thoroughly sampled and closely examined to exclude the possibility of malignant transformation.

Keywords Carcinoma ex pleomorphic adenoma · Carcinoma ex mixed tumor · Malignant mixed tumor · Nasal cavity · Nasal septum

Introduction

It is relatively uncommon for pathologists to encounter neoplasms of the nasal cavity, and diagnosing these lesions can be challenging due to the extreme diversity of tumor types in this site. Tumors of surface epithelial origin are most common, but pathologists may also come across neoplasms of soft tissue/bone, hematolymphoid, neural, and seromucinous gland origin. Tumors arising from the seromucinous glands of the nasal cavity are very similar to the tumors of the major salivary glands, with benign mixed tumor (i.e., pleomorphic adenoma or PA) being the most commonly seen.

Carcinoma ex pleomorphic adenoma (CXPA) is defined as a malignant epithelial neoplasm arising from a PA [1]. CXPA is uncommon, accounting for only 3.6% of all salivary gland neoplasms and 12% of all salivary malignancies [1]. CXPA most commonly occurs in the parotid gland, but occasionally can be seen in the minor salivary glands [1]. CXPA of the nasal cavity, however, is exceedingly rare, with only three histologically confirmed

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cases previously published [2, 3]. We report two additional cases and present a review of the literature.

Case Reports

Case 1

The patient was a 62-year-old woman from Puerto Rico who presented with a history of intermittent nasal obstruction and epistaxis of approximately 1 year's duration. Physical examination revealed a friable mass almost completely filling the left nasal passage and markedly

deviating the septum to the right. A computed tomography (CT) scan showed a large expansive lesion arising from the anterior floor of the nose. Biopsy of the mass revealed adenoid cystic carcinoma, and a partial maxillectomy was performed.

On gross examination, the tumor ($3 \times 2 \times 2$ cm) was fungating, partially ulcerated, and had a white and fleshy cut surface upon sectioning. On microscopic examination, the tumor had a predominant appearance classic for adenoid cystic carcinoma, with tubules and cribriforming structures lined by small cells with scant cytoplasm and hyperchromatic, angulated ("carrot-shaped") nuclei (Fig. 1d, f). In many foci, two cell layers were apparent.

Fig. 1 Case 1. **a–c** In the background of this tumor were several foci of bland myoepithelial cells and occasional ducts set in a chondromyxoid stromal matrix, classic for benign pleomorphic adenoma (hematoxylin and eosin, $\times 100$ [**a**], $\times 200$ [**b**], and $\times 400$ [**c**]). **d**, **e** Other areas of the tumor were classic for adenoid cystic carcinoma,

with cribriform architecture and hyperchromatic, angulated nuclei (hematoxylin and eosin, $\times 200$ [**d**] and $\times 400$ [**e**]). **f** The carcinomatous component of the tumor was widely invasive into surrounding tissues, with foci of perineural invasion (*arrow*) (hematoxylin and eosin, $\times 400$)

Scattered among the areas of adenoid cystic carcinoma, however, were foci of bland cells and tubules embedded in a chondro-myxoid matrix characteristic of PA (Fig. 1a–c). The adenoid cystic carcinoma was highly infiltrative of the surrounding tissue, and showed several foci of perineural invasion (Fig. 1f). The surgical margins were microscopically negative for tumor, with carcinoma extending to within 0.1 cm from the closest margin. This juxtaposition of adenoid cystic carcinoma in association with areas of benign mixed tumor was diagnostic for CXPA.

The patient was lost to follow-up after 1 month. At her last clinic visit, the patient was planning to receive

radiotherapy at a different institution and then return home to Puerto Rico.

Case 2

The patient was a 41-year-old woman who presented with a 5-year history of right-sided nasal congestion, obstruction, rhinorrhea, change in voice, and postnasal drip with halitosis. Physical examination revealed flexion of her nasal septum to the left side, a prominence to the outer portion of her right nose near the upper lateral cartilage, and a pedunculated mass inside her right naris. Imaging studies,

Fig. 2 Case 2. **a** The gross appearance of this tumor was that of a polypoid, well-circumscribed, tan-white mass arising from the nasal septum. **b–d** Scattered among the tumor were areas of bland myoepithelial cells and occasional ducts set in a chondro-myxoid stromal matrix, diagnostic of pleomorphic adenoma (hematoxylin and eosin, $\times 200$ [**b**, **c**], $\times 400$ [**d**]). **e** There were areas of transition from

pleomorphic adenoma (*left*) to carcinoma with hyperchromatic atypical nuclei evident even at this power (*right*) (hematoxylin and eosin, $\times 200$). **f** The frankly malignant areas consisted of back-to-back glands and trabeculae of cells with pleomorphic, hyperchromatic nuclei with prominent nucleoli, and numerous mitotic figures/apoptotic bodies (hematoxylin and eosin, $\times 400$)

including CT, positron emission tomography (PET), and magnetic resonance imaging (MRI), revealed a solitary right-sided soft-tissue nasal mass near the right nasal antrum, mechanically displacing neighboring structures. The initial biopsy was reported as a benign nasal polyp, likely due to sampling. The patient underwent elective excisional biopsy, which revealed malignant pathology with indeterminate surgical margins. The patient subsequently underwent re-excision of the mass with rib costochondral composite graft reconstruction of the nasal septum.

Gross examination revealed a well-circumscribed $2.5 \times 1.8 \times 1.0$ cm mass protruding from the right nasal septum (Fig. 2a) that was pink to tan on cut section. Histologic sections showed a tumor with a biphasic appearance, with alternating benign and malignant-appearing zones. The benign component consisted mostly of bland myoepithelial cells and occasional tubules embedded in a chondro-myxoid matrix (Fig. 2b–d), typical of PA. Occasional areas had increased cellularity and more tubule formation. These benign-appearing areas abruptly transitioned to back-to-back tubules and trabeculae of frankly malignant cells with hyperchromatic, pleomorphic nuclei and a markedly elevated mitotic rate (Fig. 2e, f). The malignant component infiltrated beyond the pleomorphic adenoma into the surrounding tissues; of note, perineural invasion was not identified. In a few foci, the carcinoma reached the overlying surface epithelium, inducing a pseudoepitheliomatous hyperplasia. The surgical margins were negative for tumor, with the carcinoma approaching within 0.3 cm of the closest margin. As the malignant component was gland-forming but did not morphologically fit into any well-defined tumor category, it was classified as high-grade adenocarcinoma, not otherwise specified (NOS). Its association with PA was diagnostic for CXPA.

The patient has followed-up in clinic several times since undergoing surgery nearly 4 months prior, and has not experienced any post-operative complications. Because of close surgical margins and concern for local recurrence, the patient underwent electron beam radiation therapy using a 12 MEV electron beam to the tumor bed. She received 50 grey in 33 fractions.

Discussion

Pleomorphic adenoma (PA) is the most common salivary gland tumor [4]. While most arise in the parotid gland, PA is also the most frequent tumor of the minor salivary glands and seromucinous glands of other organs (e.g. oral cavity, trachea, nasal cavity). PAs of the nasal cavity typically involve the nasal septum of patients with an average age of 42 years and no sex predilection [5]. Nasal PAs behave in an entirely benign fashion [5].

About 6% of all PAs harbor malignancy, most often in the form of CXPA [6]. Interestingly, although CXPAs most often occur in the parotid gland, they occur in minor salivary glands with greater frequency than would be expected by the rate of PA occurrence [7]. CXPAs have a female predominance, and occur in patients who are, on average, about 12 years older than patients with PAs [7, 8]. The two classic clinical presentations of CXPA are (1) recent rapid growth in a longstanding tumor, and (2) multiple resections of a PA with eventual malignant transformation [1, 7]. Any salivary carcinoma type can arise in a PA, but high-grade adenocarcinoma NOS and salivary duct carcinoma are the most common [1, 7, 8]. Very often, the PA component is associated with zones of hyalinizing fibrosis [1, 7, 8]. CXPAs are sub-classified as noninvasive, minimally

Table 1 Summary of all reported cases of carcinoma ex pleomorphic adenoma arising in the nasal cavity

Reference	Age (years)	Ethnicity	Gender	Tumor Size (cm)	Tumor laterality	Site of tumor origin	Presenting symptom(s)	Carcinoma subtype	Follow-up data
Cho et al. [3]	51	Asian	F ^a	2.5	Right	Nasal septum	Epistaxis	High grade adenocarcinoma, NOS ^b	10 month follow-up; free of disease
	48	White	F	NR	Left	Nasal septum	Headaches	NR ^c	1 month follow-up; free of disease
Freeman et al. [2]	66	White	F	NR	Right	Nasal septum	Obstruction	Adenoid cystic	Died of disease 12 months later
Present report	62	Hispanic	F	3	Left	Nasal floor	Epistaxis, obstruction	Adenoid cystic	1 month follow-up; free of disease
	41	White	F	2.5	Right	Nasal septum	Obstruction	High grade adenocarcinoma, NOS	Nearly 4 month follow-up; free of disease

^a F Female, ^b NOS not otherwise specified, ^c NR not reported

invasive, and invasive based on the extent of invasion by the carcinoma beyond the PA [1]. This distinction becomes very important for determining the patient's prognosis and guiding appropriate therapy; while non-invasive and minimally invasive CXPA only rarely behave in a malignant fashion [9], invasive CXPA has an overall 5-year survival of approximately 30% [10].

CXPA is regarded as the rarest of all malignancies of the sinonasal tract, to the extent that it has been called a "medical curiosity" [3]. There have been only three prior well-documented cases [2, 3]. An additional case by Chimona et al. [11] was reported as a nasal mucoepidermoid carcinoma ex-PA presenting in a male patient, but in this report there was insufficient photomicrographic evidence presented to support this diagnosis. Table 1 summarizes all the published cases of this entity in addition to our two cases. Although the number of total cases (5) is admittedly small, some interesting trends are notable. Like CXPA in general [7] but unlike benign PA of the nasal cavity [5], there is a female predominance of nasal CXPAs with all cases having presented in women. Like benign PA of the nose [5], most (4/5) cases of nasal CXPA involved the nasal septum and the most common clinical presentation was obstruction. The average age of the affected patients was 57.5 years, about 15 years older than the average age of patients with benign PA of the nasal cavity [5]. There was a slight predominance of right-sided lesions (3:2). Unfortunately there are too few cases with follow-up to make any meaningful conclusions about the clinical behavior of nasal CXPA and whether the WHO subclassification scheme (i.e. noninvasive, minimally invasive, or invasive) is useful in that setting.

The nasal CXPA cases differ from CXPAs as a whole in a few interesting ways. Not surprisingly, the most common presenting symptoms of CXPA in the nasal cavity were obstruction and epistaxis, but none of the affected patients had one of the "classic" clinical histories of CXPA (i.e., multiple recurrences or recent growth of a longstanding mass). Also, neither of our cases had the classic histologic feature of dense fibrosis or hyalinization in the PA component; this feature was described in only one of the other three previously published cases [2]. Although CXPAs are generally larger than benign PAs [7], the three cases where size was reported averaged 2.67 cm, essentially identical to the average size of benign PA of the nasal cavity (2.6 cm) [5]. Also, while benign PAs of the nasal cavity are often very cellular [5], the PA component of nasal CXPAs was dominated by a myxoid to chondro-myxoid stroma in four

of the five cases [3]. Finally, it is interesting that adenoid cystic carcinoma, an uncommon malignancy to evolve from PAs in other sites, represents 40% of the reported cases of CXPA in the nasal cavity.

In conclusion, CXPA of the nasal cavity is rare, but does occur. Moreover, nasal CXPAs will not necessarily have the classic clinical or full pathologic features characteristic for CXPA at other sites that would normally alert the clinician of the possibility of this diagnosis. As a result, PAs of the nasal cavity should be well sampled grossly and closely examined microscopically to exclude the possibility of CXPA.

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