Clinical Case Report

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Pedunculated carcinoma ex pleomorphic adenoma of the nasal cavity

A unique case report

Po-Wu Liao, MD[a], Yen-Lin Chen, MD[b,c], Jeng-Wen Chen, MD[c,d,*]

Abstract

Background: A carcinoma ex pleomorphic adenoma (CXPA) is an epithelial malignancy arising in or from a benign pleomorphic salivary adenoma. The parotid gland is the most common location of CXPAs. Minor salivary gland CXPAs of the nasal cavity are exceedingly rare, with only 6 documented in the literature.

Methods and Result: We present a 7th case: an unusual pedunculated intranasal CXPA, which had a favorable outcome after a wide endoscopic excision and the longest follow-up period reported to date. The clinical features, immunohistochemical characteristics, treatment choices, and disease outcomes of the intranasal CXPAs reported in previous studies are also reviewed.

Conclusion: This case demonstrates the importance of considering the possibility of CXPA in the differential diagnosis of minor salivary gland malignancies in the nasal cavity.

Abbreviations: CXPA = carcinoma ex pleomorphic adenoma, PA = pleomorphic adenoma, PLGA = polymorphous low-grade adenocarcinoma.

Keywords: carcinoma ex pleomorphic adenoma, malignant mixed tumor, minor salivary gland, nasal cavity, nasal septum

1. Introduction

A carcinoma ex pleomorphic adenoma (CXPA) is an uncommon epithelial malignancy that develops in a preexisting pleomorphic adenoma (PA).[1,2] The carcinoma may arise from the epithelial or myoepithelial component (or both) of a PA. Most CXPAs occur in major salivary glands. The most frequently affected site is the parotid gland, followed by the submandibular gland.[2] The signs and symptoms most frequently encountered are a painless mass that exhibits little change over a long duration, and then exhibits sudden, rapid growth. The exact etiologic factors associated with the malignant transformation of a benign PA remain unclear. Exposure to radiation and the development or accumulation of genetic instabilities within a long-standing tumor are considered to be potential factors in this transformation.[3] The incidence of malignant transformation of persistent or recurrent PA increases from 1.5% after 5 years to 10% after 15 years.[4]

CXPAs rarely affect the minor salivary glands, constituting approximately 2.6% of all minor salivary gland tumors and 18% of all minor salivary gland malignancies.[5] Minor salivary gland CXPAs often develop in the oral cavity and the oropharynx; the soft and hard palate are the most common sites.[6–10] In addition to these locations, CXPAs have been reported in the buccal mucosa,[11] the upper lip,[12] lacrimal gland,[13] and nasal cavity.[14] Unusual sites of CXPAs, such as the trachea[15] and breast,[16] have also been described.

Tumors arising from the seromucinous glands of the sinonasal region are histologically similar to tumors of the major salivary glands; however, the majority of them are malignant. Minor salivary gland tumors of the sinonasal tract generally have a favorable overall survival rate, despite a high rate of recurrence.[17] Nevertheless, minor salivary gland malignancies of the sinonasal tract have a poorer prognosis compared with their oral cavity counterparts because of their different biological behavior, a higher incidence of more aggressive adenoid cystic carcinoma, the complex anatomy of their location, and a relative delay in their diagnosis. CXPA is considered to be the rarest of all cancers of the sinonasal region.[14] Similar lesions in the nasal cavity have been regarded as "medical curiosities."[18] Only 6 cases have previously been reported in the literature.[14,19–21] In this case report, we add a unique case of CXPA that arose in the nasal cavity of a 46-year-old female patient, namely a pedunculated presentation of CXPA that had undifferentiated and squamous carcinomatous components as malignancies. This case entailed a 24-month follow-up after a wide endoscopic excision and had a favorable clinical outcome.

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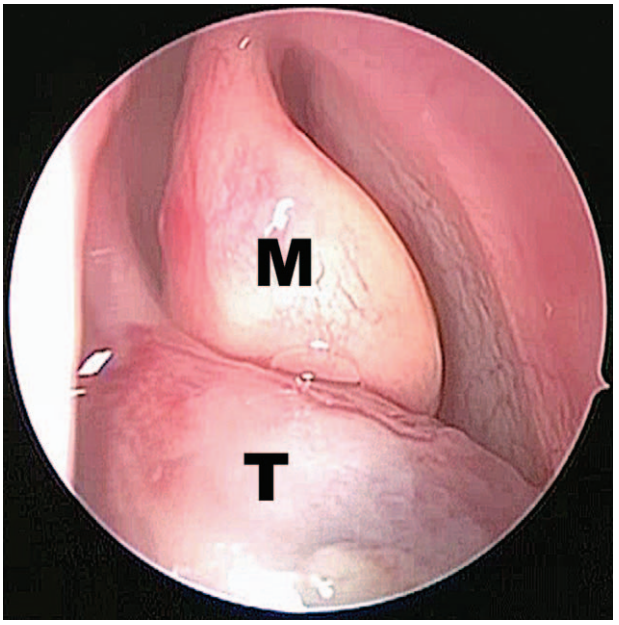

Figure 1. . Nasal endoscopic examination revealed a pedunculated tumor arising from the left nasal septum. M = middle turbinate, T = tumor.

2. Case report

A 46-year-old woman presented to an otorhinolaryngology department with intermittent left-sided epistaxis for 1 month. She reported no headache, facial pain, facial paresthesia, or visual changes. She had no history of exposure to radiation or trauma to the nose. Anterior rhinoscopy revealed a hemorrhagic mass partially occupying the left nasal cavity. No enlarged cervical lymph nodes were noted, and the remaining physical examination was unremarkable. Nasal endoscopy revealed a well-defined, solitary, irregular-surfaced, friable mass that exhibited contact bleeding and was located in the left nasal cavity. A mucosal stalk anchored the mass to the nasal septum (Fig. 1). Computed tomography revealed an expansile soft tissue mass 1.8 cm in diameter at the anterior part of the left nasal cavity without destruction of the surrounding bone structure (Fig. 2). The patient underwent an endoscopic excision. The surgical specimen ($2.2 \times 1.5 \times 1.3$ cm) was a pedunculated, well-circumscribed, encapsulated, myxoid, rubbery mass that exhibited a fleshy cut surface upon sectioning (Fig. 3A). Microscopic examination produced biphasic epithelial images that showed an admixture of surface neoplastic squamous epithelial cells and underlying mixed components of spindle- to polygonal-shaped pleomorphic myoepithelial cells and myxoid stroma (Fig. 3B). The surface squamous epithelium showed hyperchromatic and pleomorphic

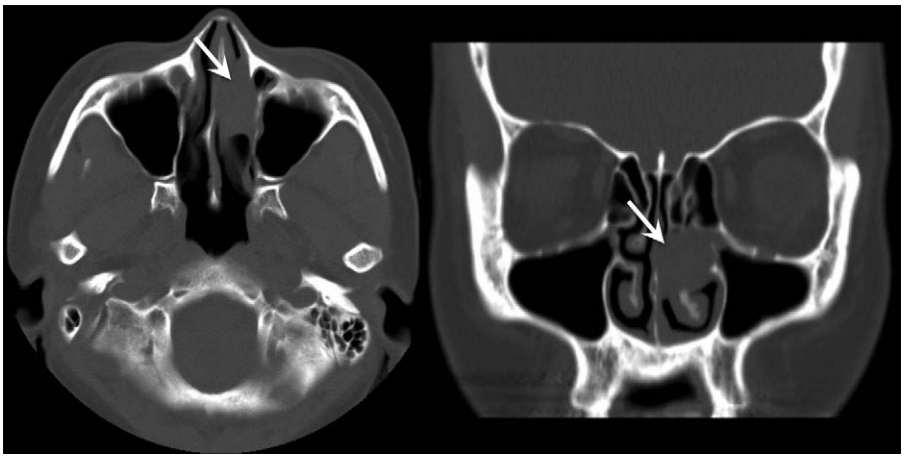

Figure 2. . Axial and coronal noncontrast computed tomographic image of the nose and paranasal sinuses showing an expansile soft tissue mass in the left nasal cavity (white arrows).

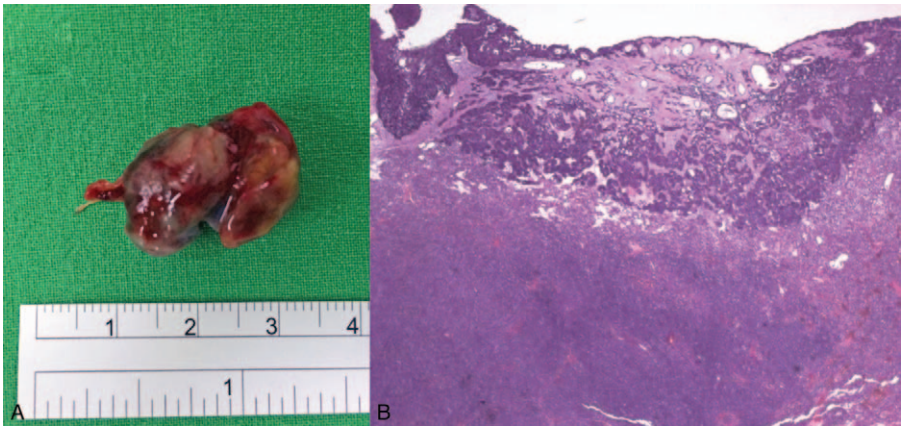

Figure 3. . Gross anatomy and histopathology. (A) Clinical image of the surgical specimen. (B) Microscopic examination revealed the heterogeneity of the tumor (hematoxylin and eosin, ×40).

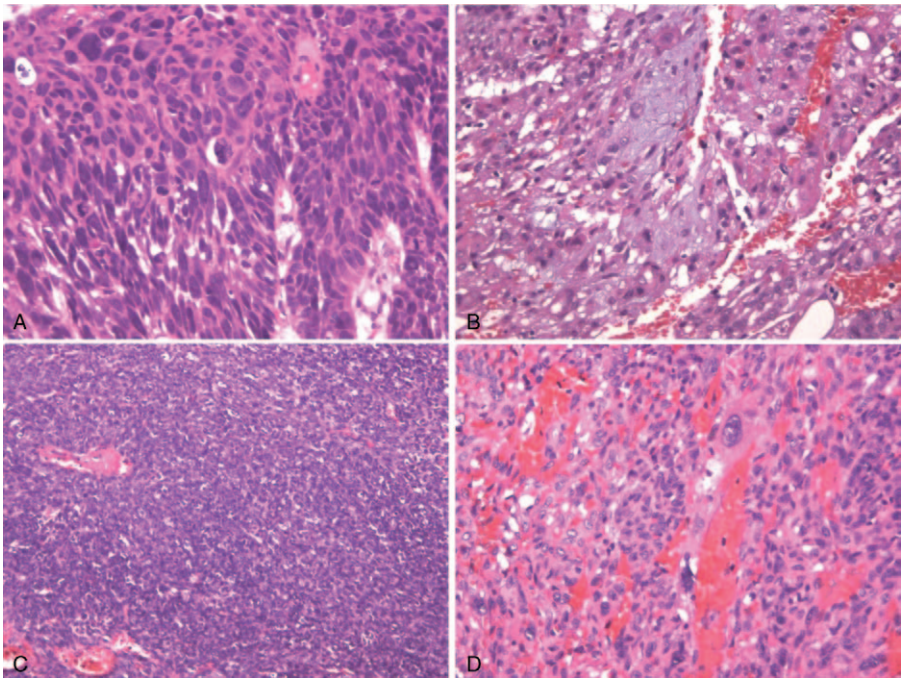

Figure 4. . (A) The surface squamous epithelium showed hyperchomatic and pleomorphic neoplastic cells (×200). (B) Myxoid stroma with relatively bland-looking nuclei was noted in the adjacent part of the neoplasm (×200). (C) The cellular solid area of the underlying carcinoma ex pleomorphic adenoma was composed of hyperchromatic cells (×100). (D) Some foci displayed a loose hemorrhagic pattern with occasional enlarge pleomorphic neoplastic cells (×200).

cells with the immunoreactivity for p63, which were identified as squamous cell carcinoma. The underlying mixed components showed that some foci of the epithelial cells abruptly transitioned to neoplastic cells that had an increased nuclear-cytoplasm ratio, a markedly elevated mitotic rate (4–5/10 high-power field), and highly pleomorphic hyperchromatic nuclei arranged in either solid or loose hemorrhagic patterns (Fig. 4A–D). However, myxoid stroma could still be seen in some small foci. The surface neoplastic squamous epithelium was immunoreactive for p63 and BCL-2 but the underlying different patterns of neoplasms were immunoreactive for CK7, Vimentin, p63, BCL-2, GFAP, and SMA (Fig. 5A–F). Because of the mixed epithelium and myoepithelium and the presence of the myxoid stroma, CXPA was diagnosed. We performed a wide endoscopic excision of the

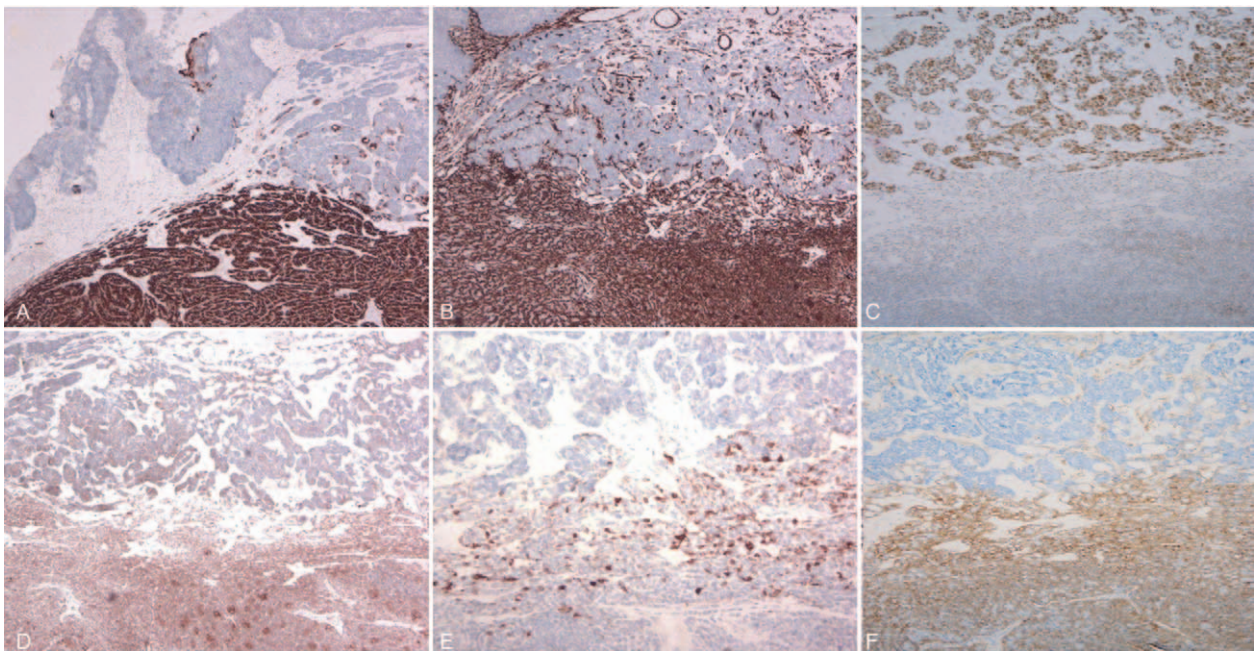

Figure 5. . Immunostain results in the neoplasm. (A) CK7, (B) Vimentin, (E) GFAP, and (F) SMA were negative in the surface squamous carcinoma but positive in the underlying CXPA. However, (C) p63 and (D) BCL-2 were immunoreactive in both the surface squamous carcinoma and underlying CXPA. CXPA = carcinoma ex pleomorphic adenoma.

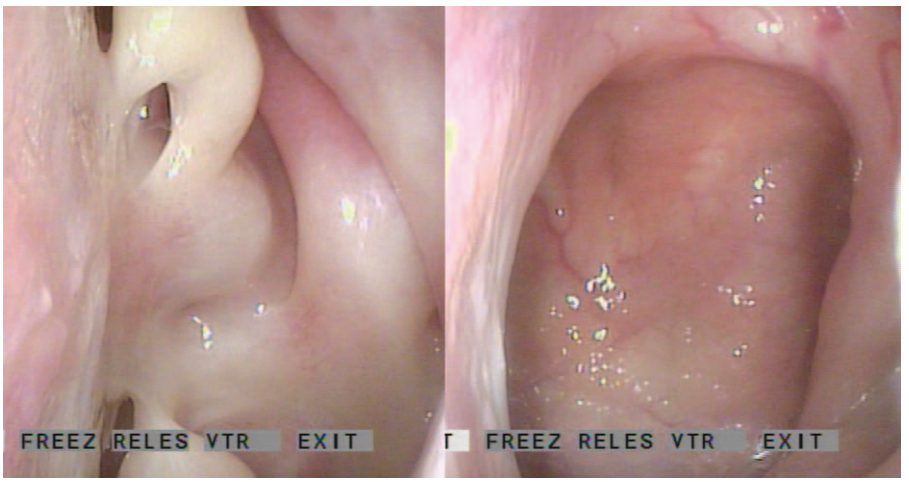

Figure 6. . Nasal endoscopy produced no evidence of local recurrence 24 months after surgery.

remaining mucoperichondrium of the nasal septum and a subsequent left middle turbinectomy. A residual tumor was found in the nasal septum, measuring $0.2 \times 0.2 \times 0.15$ cm, with a depth of 0.15 cm. The surgical margins were microscopically negative for tumor cells; the carcinoma extended to within 0.2 cm of the closest margin. The postoperative course of the patient was uneventful. The patient received no adjuvant therapies and no signs of recurrence or distant metastasis were observed after 24 months of follow-up (Fig. 6). Written informed consent was obtained from the patient. The ethics committee of the Cardinal Tien Hospital approved the study.

3. Discussion

The term "malignant mixed tumor" can refer to 3 different subtypes, namely CXPAs, true malignant mixed tumors (carcinosarcomas), and metastasizing mixed tumors.[22] Most cases, such as that of our patient, belong to the first category. A CXPA is a malignant epithelial neoplasm arising in a benign tumor (PA). Tumors of this variety constitute approximately 3.6% to 4% of all salivary gland neoplasms and 12% of all salivary gland malignancies.[19,23] Although most CXPAs occur in the major salivary glands, typically in the parotid gland, cases arising from the minor salivary glands of the oral cavity and oropharynx account for approximately 17.5% of the Armed Forces Institute of Pathology series. CXPAs are subclassified into 3 main categories by the World Health Organization on the basis of the degree of invasion of the carcinoma beyond the PA capsule, namely invasive (>1.5 mm invasion from the tumor capsule into adjacent tissues), minimally invasive ($\leq$1.5 mm penetration of the malignant component into extracapsular tissue), and noninvasive. Di Palma[24] proposed an alternative classification of CXPAs into 2 clinically relevant categories: early CXPAs and widely invasive CXPAs. Widely invasive CXPAs include any CXPA with an invasion of more than 6 mm. Early CXPAs are those that exhibit mostly favorable clinical behavior.

A CXPA is diagnosed by examination under a microscope, in addition to the consideration of patient history. The presence of an infiltrative and destructive growth pattern of carcinoma in juxtaposition with a PA is the diagnostic criterion for CXPA. In approximately 75% of cases, CXPAs arise in a PA that is apparent in the surgical specimen. However, the proportion of the malignant component varies widely, and in certain instances, ascertaining the location of the original benign PA is difficult. Diagnosis of a CXPA depends on a careful sampling of the tumor after resection to locate any coexisting benign adenomatous component. The malignant components most commonly observed in CXPAs are adenocarcinomas (not otherwise specified).[23] Almost all other malignant varieties of salivary gland tumors have been described (e.g., undifferentiated carcinoma, squamous cell carcinoma, mucoepidermoid carcinoma, salivary duct carcinoma, adenoid cystic carcinoma, small cell carcinoma, and myoepithelial carcinoma).[25] Until the past decade, the genuine malignancies of these early changes in PAs were confirmed using immunohistochemical and molecular genetic analysis of the human epidermal growth factor receptor 2 (HER-2) and TP53 genes. HER-2 and TP53 genes and proteins are involved in the early stages of the malignant transformation of PAs. Furthermore, the immunohistochemical overexpressions of HER-2, p53 protein, and the Mib-1 proliferation marker could be used as targets to identify malignant areas in PAs.[24]

CXPAs of the nasal cavity are exceedingly rare, with only 6 prior cases documented in the literature (Table 1).[14,19–21] The most common presenting symptoms in the reported cases are intermittent nasal bleeding and unilateral nasal obstruction. No cervical nodal metastasis has been described in these case reports. The average age of the affected patients was 55.7 years, approximately a decade older than the average age of patients with PA of the nasal cavity.[26] All reported cases have involved a surgical procedure as an initial treatment modality, such as a wide excision through lateral rhinotomy, partial or medial maxillectomy, or craniofacial resection. However, the unique presentation of a pedunculated, well-encapsulated nasal mass in our patient resulted in our utilizing a wide endoscopic excision. In a recent meta-analysis, Rawal et al demonstrated that the overall 2- and 5-year survival rates associated with endoscopic removal of sinonasal malignancies were comparable to, and sometimes greater than, those published for the open resection of sinonasal malignancies.[27] The survival rates of endoscopic endonasal resection seemed to correlate more strongly with cancer grading than with cancer staging. On the basis of a retrospective study, Chen et al[28] proposed that surgery followed by postoperative radiation therapy should be the standard of care for patients with CXPA of the parotid gland. However, this conclusion may not

Table 1

Summary of all reported cases of intranasal carcinoma ex pleomorphic adenoma.

Reference	Age, y/sex	Ethnicity	Size, cm	Laterality	Presenting symptom(s)	Origin	Treatment procedure (s)	Histologic subtype (s) of the carcinoma	Follow-up period
Cho et al[14]	51/F	Asian	2.5	R	Epistaxis	Nasal septum	Lateral rhinotomy, wide excision	Poorly differentiated adenocarcinoma	10 mo, free of disease
	48/F	Caucasian	NR	L	Pulsatile headaches	Nasal septum	Wide excision	NR	1 mo, free of disease
Freeman et al[21]	66/F	Caucasian	NR	R	Nasal obstruction	Nasal septum	Craniofacial resection, adjuvant radiotherapy	Adenoid cystic, squamous cell carcinoma	Died of disease 12 mo later
Chimona et al[20]	76/M	Caucasian	NR	R	Epistaxis, nasal obstruction	Lateral nasal wall	Lateral rhinotomy, medial maxillectomy	Mucoepidermoid, squamous cell carcinoma	Died of CVA complicated with aspiration pneumonia 4 mo later
Cimino-Mathews et al[19]	62/F	Hispanic	3	L	Epistaxis, nasal obstruction	Nasal floor	Partial maxillectomy	Adenoid cystic carcinoma	1 mo, free of disease
	41/F	Caucasian	2.5	R	Nasal obstruction	Nasal septum	Wide excision, adjuvant radiotherapy	High-grade adenocarcinoma, NOS	4 mo, free of disease
Present report	46/F	Asian	2.2	L	Epistaxis	Nasal septum	Wide endoscopic excision	Undifferentiated, squamous cell carcinoma	24 mo, free of disease

CVA = cerebrovascular accident, F = female, L = left, M = male, NOS = not otherwise specified, NR = not reported, R = right.

apply to intranasal CXPAs because of the different biological behavior of the sinonasal tract and a high degree of heterogeneity in cancer subtypes. Therefore, only 2 out of the 7 documented cases of intranasal CXPAs have involved adjuvant radiotherapy. Because of the short follow-up period of the reported cases, the role of postoperative radiotherapy in the prognosis of intranasal CXPAs is inconclusive. However, although the number of cases is small, notable trends can be observed. CXPAs mainly affect women, and 6 out of the 7 reported cases of intranasal CXPAs, including that of our patient, presented in women. Most cases (5 out of 7) of intranasal CXPA involved the nasal septum, and only 1 case originated in the lateral nasal wall[20]; the other case originated in the nasal floor.[19] Moreover, the malignant component of CXPAs found in the nasal cavity apparently tends to consist of various combinations of differentiations. For instance, Freeman et al[21] reported a case of intranasal CXPA involving the presence of adenoid cystic and squamous carcinomatous differentiation. Chimona et al[20] presented another case of nasal CXPA that exhibited squamous and mucoepidermoid carcinoma. In the present case, we identified both undifferentiated and squamous carcinomatous components in the surgical specimen. CXPAs with double differentiation of the carcinomatous component have also been reported in minor salivary gland CXPAs arising from the palate[7] and buccal mucosa.[29] However, the relevance of this histopathological feature remains unclear.

Histopathological factors relating to the prognosis of CXPAs were discussed by Weiler et al.[30] However, whether intranasal CXPAs share the same prognosis significance is uncertain, because an insufficient number of cases with long-term follow-up have been reported to lead to any meaningful conclusions about their clinical behavior. Because of close margins and concerns about local recurrence, postoperative radiation therapy was advised for our patient; nevertheless, she chose close follow-ups instead of receiving adjuvant radiation therapy. No evidence of local recurrence or distant metastasis was found after 24 months of follow-ups.

Although CXPA was diagnosed in the present case, the mixed patterns and immunoreactive results were notably unusual. The main differential diagnosis was polymorphous low-grade adenocarcinoma (PLGA) because of the different patterns in the tumor. PLGA is characterized by invasive growth, morphological diversity, and cytological uniformity. The morphological patterns typically include lobular solid nests admixed with cribriform, trabecular, and focal papillary cystic areas. The ductal elements are usually small and appear single layered. The tumor stroma is composed of fibrous tissue that shows varying degrees of hyalinization and myxoid change. Stromal mucinosis and elastosis may be observed along with intratumoral hemorrhage. However, the chondromyxoid matrix that typifies PA is absent. Although many factors of CXPA and PLGA overlap, the presence of myxoid stroma, immunoreactivity for GFAP, and an apparent mixture of surface carcinoma types contributed to the final diagnosis of CXPA. In summary, we present a rare case of pedunculated intranasal CXPA with a favorable outcome after a wide endoscopic excision and the longest follow-up period published to date. This case demonstrates the importance of considering the possibility of CXPA in the differential diagnosis of minor salivary gland malignancies in the nasal cavity. We identified a predominance of cases in women, a tendency to originate in the nasal septum, and the characteristic of double differentiation of the carcinomatous component of the reported intranasal CXPAs. Because of their extremely low incidence, information about the natural course, prognosis, and treatment of intranasal CXPAs can currently be extrapolated from the published data regarding tumors of the same type that are located in the major salivary glands.

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