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Original Article

Carcinoma ex Pleomorphic Adenoma: A Case Series and Literature Review

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Abstract

Introduction

Carcinoma ex pleomorphic adenoma (CXPA) is a rare malignant salivary gland tumor that can lead to severe complications and carries a risk of distant metastasis. This study aims to provide a comprehensive overview of CXPA through a case series and a review of the literature.

Methods

This was a single-center retrospective case series. The patients were included from November 2018 to December 2024. All confirmed cases of CXPA that were diagnosed and managed with complete clinical data were included in this study. Cases with incomplete data were excluded.

Results

Six patients were included, with ages ranging from 45 to 88 years (mean ± SD: 64 ± 15.36; median: 62). Most were male (66.7%), with an even distribution of occupations. All presented with preauricular swelling lasting 2 to 10 years, and three had left-sided tumors. Fine needle aspiration identified 33.3% as benign and 16.7% as malignant. Ultrasound examination showed solid tumors in four cases, three of which were well-defined. Three (50%) underwent total parotidectomy, and three (50%) underwent superficial parotidectomy. Histopathological examination revealed adenocarcinoma ex pleomorphic adenoma in 50% and squamous cell carcinoma ex pleomorphic adenoma in 16.7%. Tumor sizes ranged from 3.5 to 6 cm (mean: 4.73 ± 1.24 cm). Capsular invasion was present in all cases, with lymph node involvement in 33.3%, lympho-vascular invasion in 16.7%, and perineural invasion in 50%. Adjuvant therapy included radiotherapy or chemoradiotherapy.

Conclusion

Although CXPA is very rare, it is a serious condition; surgical approach with or without adjuvant therapy may result in preferable outcomes.

1. Introduction

Salivary gland tumors are uncommon neoplasms of the head and neck region. Among them, pleomorphic adenoma is the most prevalent benign type, accounting for approximately 70% of all salivary gland tumors [1]. The parotid gland is the most frequent site of occurrence for salivary gland tumors, followed by the submandibular gland and the minor salivary glands [2]. If left untreated, pleomorphic adenoma carries a risk of malignant transformation, with the risk reaching up to 9.5% after 15 years and continuing to increase over time [3].

Carcinoma ex pleomorphic adenoma (CXPA) is a rare malignant salivary gland tumor that develops from a pre-existing benign pleomorphic adenoma, accounting for approximately 5% of all head and neck malignancies [4]. CXPA constitutes approximately 3.6% of all salivary gland neoplasms, 6.2% of all mixed tumors, and 11.6% of all malignant salivary gland neoplasms. This malignancy predominantly occurs between the sixth and eighth decades of life and shows a slight female predominance [5]. Historical data reveal geographical variation in the incidence of this tumor relative to primary parotid malignancies, with reported rates of 12–13% in the United States, 14% in Switzerland, and up to 25% in the United Kingdom [1]. CXPA has also been referred to by other names, including carcinoma ex mixed tumor, carcinoma ex adenoma, and carcinoma ex benign pleomorphic adenoma [5].

The risk of malignant transformation is heightened by patient-related factors such as advanced age and a history of smoking, as well as disease-related factors, including larger tumor size and higher histological grade [1]. As a rare and complex disease, the clinical and pathological understanding of CXPA continues to evolve with ongoing research and advancements in diagnostic techniques [1]. This study aims to provide a comprehensive overview of CXPA by analyzing six cases, with a focus on clinical presentation, diagnostic approaches, treatment outcomes, and a review of the literature. The references have been evaluated for credibility using the most up-to-date criteria [6].

2. Methods

2.1. Study design

This single-center case series included consecutive patients diagnosed with CXPA who were treated between November 2018 and December 2024.

2.2. Data collection

After de-identification, the necessary data were retrospectively obtained from patient records in the Head and Neck clinic database. Extracted variables included patient demographics, occupation, clinical presentation, ultrasound (U/S) findings, treatment approach, outcomes, histopathological findings, and follow-up information. The follow-up period ranged from 1 to 5 years.

2.3. Eligibility criteria

All confirmed cases of CXPA that were diagnosed and managed with complete clinical data were included in this study. Cases with incomplete data were excluded.

2.4. Intervention

All patients underwent a thorough preoperative assessment, including a detailed clinical examination with an emphasis on facial nerve function, as well as imaging to assess lesion size, location, extent, and potential local invasion. Surgical procedures were performed under general anesthesia with the patient positioned supine and the head turned contralaterally to the lesion side. A standard Blair (lazy-S) incision was utilized, beginning anterior to the tragus, extending around the earlobe, and continuing into a natural skin crease in the upper neck to ensure optimal surgical access and cosmetic appearance.

Following subplatysmal flap elevation, dissection was carried out to identify the main trunk of the facial nerve, typically located at the stylomastoid foramen, just inferior and medial to the tympanomastoid suture. In cases of partial parotidectomy, only the superficial lobe of the gland was excised, preserving the facial nerve and its branches. In total parotidectomy, both superficial and deep lobes were removed, with caution to maintain all major branches of the facial nerve. Dissection proceeded using fine instruments and bipolar cautery under loupe magnification to enhance visualization and minimize nerve trauma.

Hemostasis was achieved using bipolar coagulation and ligation of feeding vessels. Redivac drains were placed in the surgical bed and secured with sutures to facilitate postoperative drainage and reduce the risk of hematoma or seroma formation. Skin closure was performed in layers using absorbable sutures for the deep plane and non-absorbable or subcuticular sutures for the skin to optimize healing and reduce scar formation.

2.5. Post-intervention considerations

Postoperatively, patients received protocol-based analgesia and prophylactic antibiotics. The diagnosis was confirmed through histopathological examination of the surgical specimens.

2.6. Statistical analysis

Data entry and coding were performed using Microsoft Excel 2019. Descriptive statistical analysis of qualitative data was conducted using the Statistical Package for the Social Sciences (SPSS) Version 25. Results were presented as means, frequencies, and percentages.

3. Results

This study included 6 patients, whose raw data are presented in Tables 1 & 2. Ages ranged from 45 to 88 years, with a median age of 62 and a mean age of 64 ± 15.36 years. Most of the patients were males (66.67%), with occupations evenly distributed (33.33% housewives, 33.33% unemployed, and 33.33% workers). Family history was unremarkable in all patients. Smoking was reported in only 1 patient. All the patients presented with preauricular swelling, with duration of symptoms

Table 1. Demographics and preoperative findings of the enrolled patients.

Case no.	Age	Sex	Occupation	Family history	Smoking	Chief complaint	Duration (years)	Site	FNAC findings	Consistency (U/S)	Size in cm (U/S)	Suspecious lymph nodes (U/S)
1	67	F	Housewife	Unremarkable	No	Pre-auricular swelling	7	LPG	SUMP	Solid, well-defined	5.1	Not seen
2	88	M	Jobless	Unremarkable	No	Pre-auricular swelling	3	LPG	AUS	Complex	6.9	Seen
3	49	M	Worker	Unremarkable	Yes	Pre-auricular swelling	6	RPG	Benign	Solid, well-defined	1.7	Not seen
4	57	F	Housewife	Unremarkable	No	Pre-auricular swelling	4	RPG	Benign	Solid, well-defined	2.9	Not seen
5	45	M	Worker	Unremarkable	No	Pre-auricular swelling	2	LPG	N/A	N/A	N/A	N/A
6	78	M	Jobless	Unremarkable	No	Pre-auricular swelling & facial palsy	10	RPG	Malignant	Solid, irregular	3.6	Seen

F: Female, M: Male, LPG: Left parotid gland, RPG: Right parotid gland, SUMP: Salivary gland Neoplasm of Uncertain Malignant Potential, AUS: Atypia of Undetermined Significance, U/S: Ultrasonography

Table 2. Treatment and outcome of the enrolled patients.

Surgical approach	HP	Tumor stage	Tumor size (CM)	LN involvement	Invasion		Adjuvant therapy	Outcome	Follow-up (years)
					Capsular	Lympho-vascular	Perineural			
Total Parotidectomy	Adenocarcinoma ex pleomorphic adenoma	pT3	5.5	N/A	FI	Not seen	Not seen	N/A	No recurrence	4
Superficial parotidectomy, suprahyoid lymph nodes dissection & excision of sublingual gland	Adenocarcinoma ex pleomorphic adenoma	pT4a N1	6	Seen	I	Not seen	Seen	Radiotherapy	Died	N/A
Superficial parotidectomy	Squamous cell carcinoma ex pleomorphic adenoma	pT2 N0	3.5	Not seen	I	Not seen	Not seen	N/A	No recurrence	5
Superficial parotidectomy	Carcinoma ex-pleomorphic adenoma	pT2 N0 R0	3.5	Not seen	FI	Not seen	Not seen	CCRT	No recurrence	2
Left total parotidectomy	Carcinoma ex-pleomorphic adenoma	pT2 N0	3.9	Not seen	FI	Not seen	Seen	CCRT	No recurrence	1
Right total parotidectomy with right cervical lymph node dissection	Adenocarcinoma ex pleomorphic adenoma	pT4a N3b R1	6	Seen	I	Extensive	Seen	CCRT	No recurrence	1

HP: Histopathology, N/A: Not available, FI: Focally infiltrative, I: Infiltrative, CCRT: Concurrent chemoradiotherapy

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ranging from 2 to 10 years. The left parotid gland was affected in 3 (50%) patients. Upon fine needle aspiration (FNA), 2 (33.33%) of the tumors were benign, while only 1 (16.67%) tumor was malignant with certainty. On U/S, 4 of the tumors were solid, 3 of which were well-defined. Lymph nodes were suspicious for involvement in 2 (33.33%) patients. three patients (50%) underwent total parotidectomy, while the other 3 (50%) underwent superficial parotidectomy. Histopathology revealed adenocarcinoma ex pleomorphic adenoma in 3 (50%) patients, and squamous cell carcinoma ex pleomorphic adenoma in 1 (16.67%) patient. Tumor sizes ranged from 3.5 to 6 cm (mean: 4.73 ± 1.24). Lymph node involvement was seen in 2 (33.33%) patients. Capsular invasion was observed in all patients, lympho-vascular invasion in 1 (16.67%) patient, and perineural invasion in 3 (50%) patients. Adjuvant therapy included radiotherapy and chemoradiotherapy (Table 3). No cases of recurrence were reported, and one patient passed away from old age.

4. Discussion

The median age of this study was 62 years, which is close to a study by Suzuki et al., which had a median age of 60 years [7]. The mean age of 64 in the current study was also comparable to other studies. For example, a retrospective study of 73 patients with CXPA had a mean age of 61 years [8]. However, a lower mean of 55.1 was reported by Seok et al. [9]. Kato et al. reported four cases, one of which involved a 48-year-old individual [3]. Recently, another case of CXPA in a 45-year-old male was also reported [10]. When compared to pleomorphic adenoma, the mean age of diagnosis is shown to be higher by 13 years [9].

The current series demonstrated a male predominance, consistent with findings from a systematic review by Key et al., in which males accounted for 58.9% of cases [1]. In this series, the parotid gland was involved in 100% of cases, higher than the

Table 3. Summary of clinical and demographic findings.

Variables	Frequency/percentage
Sex	Total (6)
Male	4 (66.67%)
Female	2 (33.33%)
Age (years) Range	45-88
Mean (±SD)	64 ± 15.36
Median (IQR)	62 (29)
Smoker	1 (16.67%)
Non-smoker	5 (83.33%)
Chief complaint	
Preauricular swelling	5 (83.33%)
Preauricular swelling & facial palsy	1 (16.67%)
Duration of symptoms (years) Range	2-10
Mean (±SD)	5.3 ± 2.69
Site	
Left parotid gland	3 (50%)
Right parotid gland	3 (50%)
Surgical approach	
Total parotidectomy	3 (50%)
Superficial parotidectomy	3 (50%)
Adjuvant therapy	
Radiotherapy	1 (16.67%)
Concurrent chemo-radiotherapy	3 (50%)
N/A	2 (33.33%)
HPE	
Adenocarcinoma ex pleomorphic adenoma	3 (50%)
Squamous cell carcinoma ex pleomorphic adenoma	1 (16.67%)
Carcinoma ex pleomorphic adenoma	2 (33.33%)
Degree of invasion	
Low degree	3 (50%)
Medium degree	1 (16.67%)
High degree	2 (33.33%)
Invasion status	
Capsular	6/6 (100%)
Lympho-vascular	1/6 (16.67%)
Perineural	3/6 (50%)
Tumor size (cm)	
Range	3.5-6
Mean (±SD)	4.73 ± 1.24
Outcome	
No recurrence	5 (83.33%)
Death	1 (16.67%)

SD: Standard deviation, IQR: Interquartile range, N/A: Not available, HPE: Histopathology

typical range reported in the literature, which may reflect referral bias. Nevertheless, the parotid remains the most commonly affected salivary gland subsite [1].

Patients presented with symptom durations ranging from 2 to 10 years, which is notably shorter than what is commonly reported in earlier literature. A comprehensive review, for example, documented a mean symptom duration of 23.3 years [5]. Longer durations reaching 50 years have also been reported [3]. However, more recent reports indicate shorter intervals; Keerthi et al. reported a case with only six months of symptoms [11]. The short symptom durations in the current study may reflect earlier detection and referral patterns or more aggressive tumor biology, leading to earlier presentation.

One of the diagnostic challenges was the low sensitivity of FNA for malignancy at 16.67%, which is a known limitation of FNA in CXPA diagnosis. In a series of 16 patients, only seven (43%) were identified as malignant [12]. In a cohort of 260 patients, 170 patients (65.4%) had a preoperative FNA. In 156 of those (91.8%), the FNA diagnosed a benign tumor, with the rest having an unsatisfactory or nondiagnostic FNA [13]. Parotid FNA carries two potential sources of false-negative results: sampling a benign area of a pleomorphic adenoma rather than the malignant component, and misclassifying a low-grade CXPA as a benign pleomorphic adenoma [13].

Tumor sizes in reported cases range from 1 to 26 cm [4]. Similarly, the sizes observed in the present study fall within this typical range. A multivariate analysis has identified tumor size ≥4 cm as a factor associated with worse prognosis. Notably, six patients in the current series (66.7%) had tumors larger than 4 cm but demonstrated favorable outcomes, suggesting that effective treatment protocols may mitigate the impact of tumor size on prognosis.

Recent studies have shown that the most frequently encountered histological types in CXPA are highly malignant adenocarcinoma and undifferentiated carcinoma. However, a wide spectrum of other subtypes has also been reported, including squamous cell carcinoma, mucoepidermoid carcinoma, adenoid cystic carcinoma, papillary carcinoma, and terminal duct carcinoma [11]. In the current series, adenocarcinoma accounted for 50% of cases, while squamous cell CXPA was observed in one patient. This aligns with findings from a retrospective study of 24 patients, which reported six cases of adenocarcinoma and a single case of squamous cell carcinoma [12].

Certain pathological features, such as invasiveness, have been studied in the literature. In particular, extracapsular extension and invasion measuring ≥1.5 mm have been linked to an increased risk of recurrence and mortality [1]. Capsular invasion was present in all cases in the current series, with 50% showing focal infiltration. Lympho-vascular invasion was observed in 16.67%, and perineural invasion in 50%. Similar findings have been reported in the literature, such as Kim et al.'s study of 17 CXPA patients, where lympho-vascular invasion was seen in three patients [14]. In a cohort of 215 patients with parotid gland tumors, 14 of whom were diagnosed with CXPA, perineural invasion was documented in 21.4% [15]. In a retrospective study of 51 patients, 45.1% exhibited perineural invasion [16]. Another study involving 37 CXPA patients found 43% with perineural invasion and 40.5% with lympho-vascular invasion [17]. Perineural invasion significantly impacts distant metastasis, tumor-specific survival, and overall survival ($P < 0.05$), and tends to be associated with locoregional recurrence ($P = 0.086$). In multivariate analysis, perineural invasion is identified as an independent prognostic factor for overall survival [16].

Lymph node invasion was observed in 33.3% of the patients, which is comparable to findings from previous studies. For instance, a review involving 619 patients reported lymph node involvement, both single and multiple nodes, in 29.6% of cases [18]. Another retrospective analysis of 51 patients revealed that 33.3% of the patients had lymph node involvement [16]. In their study, Zhao et al. identified advanced T stage and lymph node involvement as important factors for an unfavorable clinical outcome [16].

Treatment of CXPA involves an ablative surgical procedure, which may or may not be followed by reconstructive surgery [5]. To date, no universally accepted treatment protocol exists for this tumor type [4]. Zhao et al. emphasized that the extent of surgical intervention should be individualized, taking into consideration the tumor's location, size, and the involvement of adjacent anatomical structures. For parotid gland tumors, a total or radical parotidectomy is generally recommended for frankly invasive CXPA, with facial nerve resection indicated if direct tumor infiltration is evident [16]. In the present series, three patients underwent superficial parotidectomy, one of whom also underwent suprahyoid lymph node dissection and excision of the sublingual gland due to regional extension, and the other three underwent total parotidectomy.

Adjuvant therapies for CXPA may include radiotherapy or chemotherapy, primarily aimed at improving local control and potentially enhancing survival outcomes [10]. However, due to the rarity of the disease, data on the specific efficacy of radiotherapy are limited [16]. In a retrospective analysis of 63 patients, Chen et al. reported that postoperative radiotherapy significantly improved local disease control, although it did not confer a clear survival benefit [19]. Chemotherapy is generally reserved for patients with advanced, recurrent, or metastatic disease and is used primarily for palliative purposes. The role of radiotherapy remains controversial and is typically considered in cases with high-grade histology, positive margins, perineural invasion, or lymph node involvement [20]. Historically, CXPA has been regarded as a high-grade malignancy, often necessitating adjuvant radiotherapy. This classification is reflected in data from a national American cancer database, which demonstrated that a higher proportion of patients with CXPA were selected to receive chemoradiotherapy [1]. Three patients received adjuvant chemoradiotherapy, all of whom had good outcomes.

Patients diagnosed with noninvasive or minimally invasive CXPA generally exhibit favorable outcomes, with low recurrence rates and minimal risk of metastasis. In contrast, those with frankly invasive tumors have a significantly poorer prognosis. Reported recurrence rates for invasive CXPA range from 23% to 50%, and distant metastases may occur in up to 70% of cases, reflecting the aggressive biological behavior of

the invasive subtype [4]. No recurrences were observed in this series. While this may indicate effective treatment approaches, it could also be due to the relatively short follow-up periods.

5. Conclusion

Although CXPAs are very rare, they are serious conditions that may originate from benign conditions. Surgical approach with or without adjuvant therapy might result in good outcomes.

Declarations

Conflicts of interest: The authors have no conflicts of interest to disclose.

Ethical approval: The study was ethically reviewed and approved by the Scientific Committee of the Kscien organization (Approval No. 2025-38).

Patient consent (participation and publication): Not applicable

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Use of AI: ChatGPT-4.0 was used to assist in language editing and improving the clarity of the manuscript. All content was reviewed and verified by the authors. Authors are fully responsible for the entire content of their manuscript.

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