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# Squamous Cell Carcinoma Ex Pleomorphic Adenoma of the Parotid Gland: Unusual Entity and Diagnostic Pitfalls

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**Abstract.** *Background: Carcinoma ex pleomorphic adenoma (PA) of the salivary gland with squamous cell carcinoma (SCC) component is extremely rare and can be easily misdiagnosed as a benign PA or SCC (primary or metastatic). Case Report: A 75-year-old male who had no significant past medical history, presented with a rapid growing right parotid gland mass. A fine needle aspiration revealed malignant cells. Following partial parotidectomy, a 2.4 cm ill-defined mass was grossly identified. Microscopically, it showed a keratinizing SCC with adjacent component of residual PA. Immunohistochemically, the malignant tumor cells were positive for p40, p63 and CK5. The residual PA was focally positive for CAM5.2, SMA, p63 and S100. The pathological features were consistent with SCC ex PA. The patient was well at the 7 month-follow-up post-surgery. Conclusion: SCC ex PA is a rare entity that can be mistaken for a benign PA with squamous metaplasia, or primary or metastatic SCC. It behaves aggressively and has high recurrence and metastasis rate. Awareness of this disease and the diagnostic pitfalls are essential to avoid misinterpretation in difficult cases.*

Carcinoma ex pleomorphic adenoma (CXPA) is defined as a carcinoma arising from a primary (de novo) or recurrent benign pleomorphic adenoma (PA) (1, 2). It accounts for 3%-5% of all salivary gland neoplasms and 12% of all salivary malignancy (2, 3). Eighty percent of CXPA occur in major salivary glands with a majority of cases noted in the parotid and submandibular glands, and 20% of cases seen in minor salivary glands (4). CXPA can be asymptomatic and has a similar clinical presentation as PA before it becomes widely invasive. Patients frequently become aware of the cancer when they experience rapid enlargement of the mass, pain, or other clinical symptoms. Facial nerve involvement is present in one third of cases (5). The clinical presentation may resemble a multiple facial nerve schwannoma. Increased preoperative duration of a PA increases the risk of malignant transformation into CXPA. Treatment for CXPA often involves a complete surgical resection followed by adjuvant radiotherapy.

The malignant components of CXPA can be divided into epithelial component only, myoepithelial component only or both, of which, adenocarcinoma not otherwise specified, and salivary ductal carcinoma are most common, but squamous cell carcinoma (SCC) is uncommon (1, 5, 6). We herein, report an extremely rare case of CXPA of the parotid gland with an unusual malignant component of SCC, review the literature, and discuss diagnostic pitfalls and prognosis.

## Case Report

A 75-year-old male with no known pre-existing PA presented with a right cheek lump that he had noticed 3 weeks earlier. A computerized tomographic (CT) scan revealed a 2.6 cm parotid mass in the superficial lobe extending to abut the retromandibular vein and an enlarged lymph node nearby (Figure 1). A fine needle aspiration of the mass identified malignant cells with squamous cell differentiation. Subsequently, the superficial lobe and portions of the deep lobe of the parotid gland were surgically removed. Macroscopically, a 2.4 cm ill-defined mass was identified. The tumor had grey-white, fibrotic cut surface. No necrosis was grossly identified. Given the squamous cell differentiation noted by fine needle aspiration, the entire specimen was submitted for histologic examination. Microscopic examination revealed an ill-defined invasive tumor composed of predominantly keratinizing squamous cells with areas of a poorly differentiated carcinoma component. Within the tumor, a 2 mm hyalinized lesion



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*Key Words:* Carcinoma ex pleomorphic adenoma, squamous cell carcinoma, parotid gland.

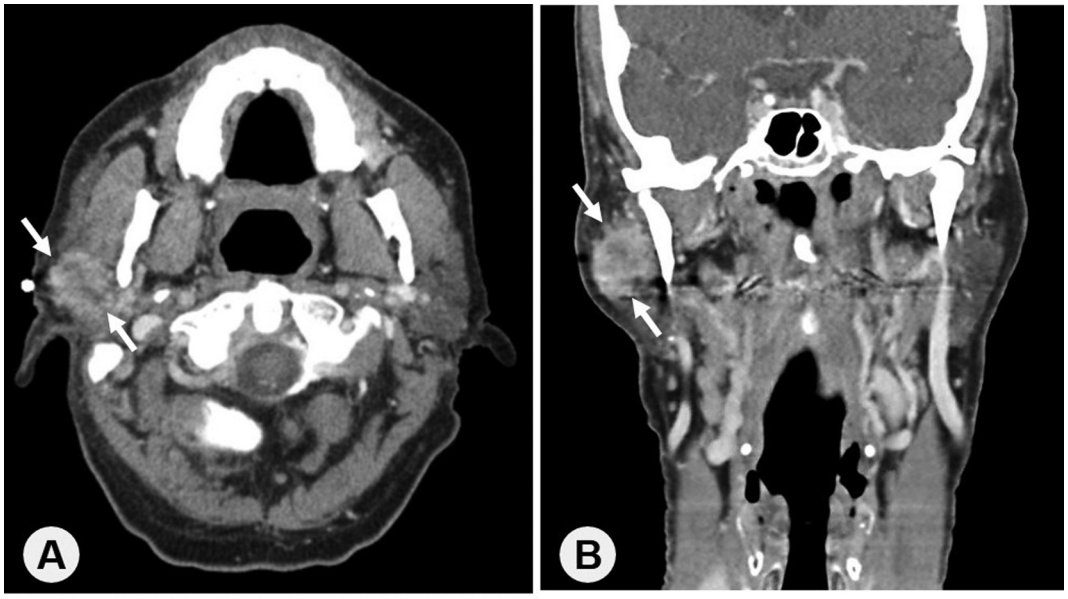


Figure 1. *Radiological findings of the right parotid gland mass. Computed tomographic scan showing a 2.6 cm parotid mass (arrows) in the superficial lobe extending to abut the retromandibular vein. (A) Axial view; (B) Coronal view.*

composed of bland epithelial cells with a focal ductal structure in a hyalinized and fibrotic stroma was identified, suggesting a typical PA (Figure 2A and B). The invasive SCC showed perineural invasion, but no lymphovascular invasion or lymph node metastasis was identified. Resection margin was involved by SCC. Immunohistochemically, all malignant tumor cells were positive for p40 (Figure 2C), p63, and CK5, whereas negative for CK7, confirming squamous differentiation. Immunohistochemical staining performed on the tiny focus of hyalinized lesion showed that the epithelial (ductal) cells were positive for CAM5.2. Some tumor cells were positive for SMA, p63, and S100, confirming the presence of myoepithelial cells (Figure 2D-F). The above findings confirmed PA of this small hyalinized lesion.

Overall, the histological features and immunoprofile supported the diagnosis of SCC ex PA, American Joint Committee of Cancer (AJCC 8$^{th}$ edition) pathologic stage pT2N0. Postoperatively, the patient underwent radiation therapy for 6 weeks because of positive margin, perineural invasion, and poorly-differentiated histology. At 7 months follow-up post-surgery, he was well with no tumor recurrence or metastasis.

## Discussion

CXPA is defined as any epithelial malignancy arising in association with benign primary or recurrent PA. Carcinoma components of CXPA are often adenocarcinoma not otherwise specified, salivary duct carcinoma, or myoepithelial carcinoma. SCC ex PA is rare. Seifert *et al*. (7) identified an SCC component in 4 out of 38 cases of CXPA. In 33 cases of CXPA reported by Suzuki *et al*. (8) and 21 cases of CXPA described by Lim *et al*. (9), only one case each was classified as SCC. In contrast, Lewis *et al*. (6) found no cases with SCC component in 73 cases of CXPA, nor did Tortoledo *et al*. (10) among 37 cases of CXPA. SCC, as the pure malignant component of CXPA, thus, seems to be rare; only a few such cases are reported to our knowledge (Table I) (11-17). In our case, a component of SCC was immediately recognized. The differential diagnosis would be metastatic SCC (more common), primary parotid gland SCC and SCC ex PA. The patient had no history of SCC, therefore metastatic SCC is unlikely. Both primary SCC and SCC ex PA in the salivary glands are extremely rare. Presence of residual PA is a key to distinguish SCC ex PA from primary SCC. In our case, with extensive sampling, a tiny focus of well-circumscribed nodule was noted within SCC, which was morphologically and immunohistochemically consistent with PA. The PA component showed extensive hyalinization, which was a significant predictor of malignant transformation in PA noted in a study of atypical mixed tumors (18).

A slow growing parotid mass that has recently exhibited a growth spurt should raise the suspicion of a malignancy (*e.g*., CXPA). CXPA can be mistaken for a benign PA. In PAs with extensive sclerosis or hyalinization, additional sampling is necessary to exclude a malignant component. It can also be misdiagnosed as another salivary gland malignancy, as carcinomas frequently overgrow and replace the benign area of PA. Molecular testing for PLAG1 and HMGA2 rearrangement

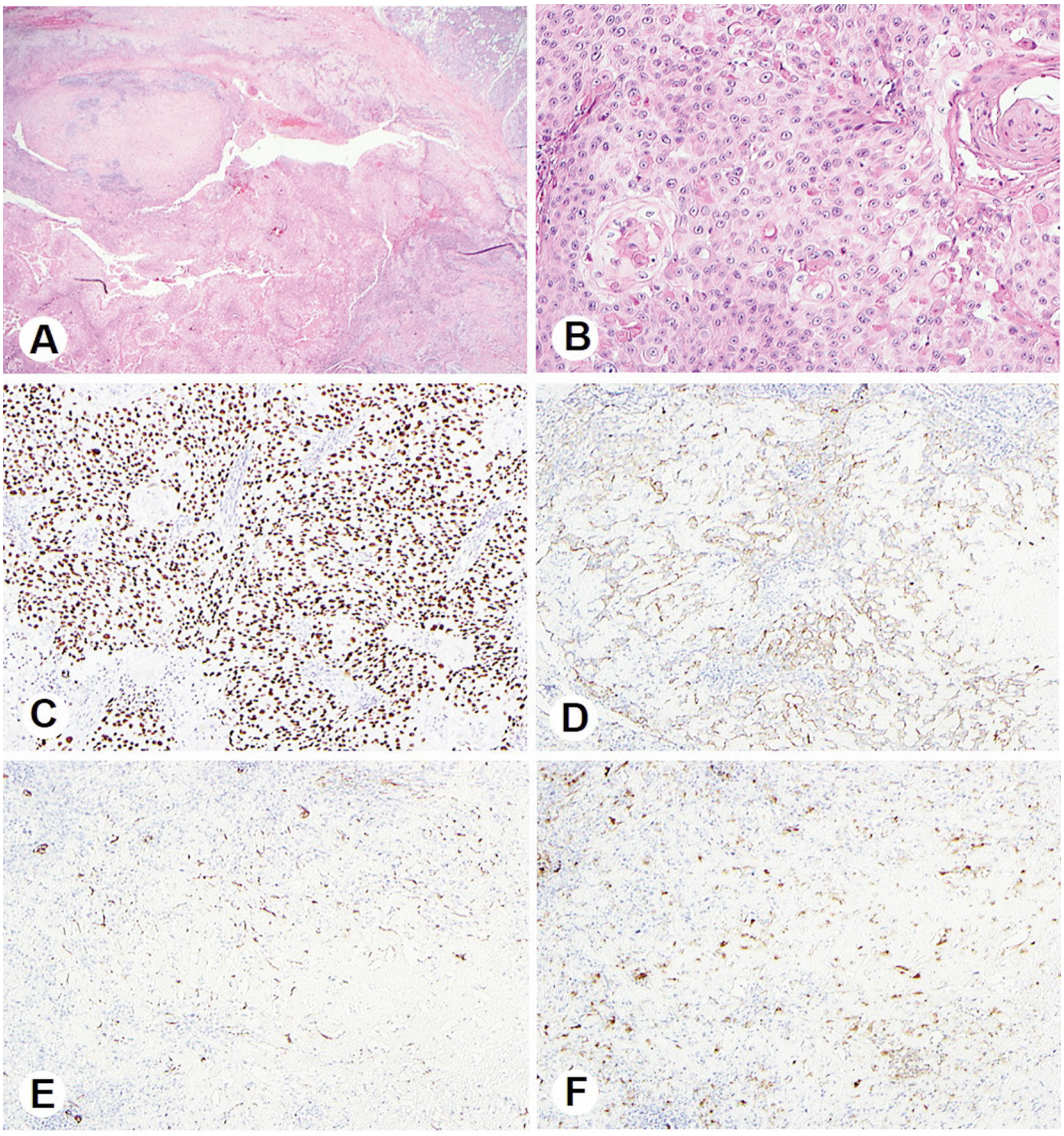


Figure 2. *Histological features and ancillary studies of the right parotid gland mass. (A) Low-power view of the tumor showing hyalinized pleomorphic adenoma (upper left) surrounded by squamous cell carcinoma and adjacent normal parotid gland tissue [hematoxylin and eosin (H&E), ×20]. (B) High-power view displaying keratinizing squamous cell carcinoma component (H&E, ×100). (C) The carcinoma component was strongly positive for p40 by immunohistochemistry (×100). (D-F) The pleomorphic adenoma cells were positive for CAM 5.2 (D), SMA (E) and S100 (F) by immunohistochemistry (×100).*

(19, 20), known as major cytogenetic abnormality in PA, may help identify previous PA. In our case, SCC was easily recognized as the malignant component, but the challenge is to determine whether it is primary or metastatic SCC. Primary SCC is extremely rare. Therefore, whenever SCC component is identified in a salivary gland, extensive tumor sampling, careful histologic assessment and scrutiny of patient's medical history are required to rule out SCC ex PA *vs*. metastasis before making a diagnosis of primary SCC.

The prognosis of CXPA is thought to be worse than that of other salivary gland malignancies, with a survival rate varying from 25% to 65% (6, 8, 9). Tumor stage, grade, extent of invasion, tumor size, proportion of carcinoma, high proliferation index, positive margin, and perineural invasion are well known significant prognostic factors (6). In addition, some studies have revealed that histologic subtype is closely related to clinical outcomes. The survival rates for patients with invasive salivary duct carcinoma or adenocarcinoma not

Table I. *Summary of reported squamous cell carcinoma ex pleomorphic adenomas including the current case.*

| Author | Case, n | Histology subtype | | | | Follow-up, years |
|---|---|---|---|---|---|---|
| | | SDC | Adenocarcinoma NOS | SCC | Others | |
| Seifert *et al*. (7) | 38 | N/A | N/A | 4 | N/A | N/A |
| Suzuki *et al*. (8) | 33 | 8 | 16 | 1 | 8 | Recurrence (11), metastasis (9), death (10), 3 years |
| Lim *et al*. (9) | 21 | 10 | 0 | 1 | 10 | Recurrence (7), metastasis (5), death (12), 68 months |
| Lewis *et al*. (6) | 73 | 24 | 31 | 0 | 18 | Recurrence (15), metastasis (66), death (36); 14 months-17 years |
| Tortoledo *et al*. (10) | 37 | 13 | 9 | 0 | 15 | Death (18) |
| Zbären *et al*. (17) | 24 | 4 | 6 | 1 | 13 | Recurrence (5), metastasis (6), death (5); 12 months-10 years |
| Ita *et al*. (16) | 1 | 0 | 0 | 1 | 0 | N/A |
| Mitate *et al*. (15) | 1 | 0 | 0 | 1 | 0 | No recurrence, 6 years |
| Current case | 1 | 0 | 0 | 1 | 0 | No recurrence, 7 months |

SDC: Salivary duct carcinoma; NOS: not otherwise specified; SCC: squamous cell carcinoma; N/A: not available.

otherwise specified was found to be significantly poorer than other subtypes (8). Loco-regional recurrence is considered to be a major prognostic factor for patients with CXPA. Olsen *et al*. noted that the prognosis after detection of progression or recurrence was poor, with a median survival of less than 1 year (5). All disease specific deaths occurred within 6 years after the initial operation.

In conclusion, SCC ex PA is a rare entity with significant clinical and pathological relevance. Awareness of this entity and its diagnosis pitfalls are critical, as patients could potentially be inappropriately discharged without follow-up if mistakenly diagnosed with a benign PA. It generally displays aggressive behavior and has high recurrence and metastatic rates. Early diagnosis, adequate removal of neoplasms and careful follow-up remain the best strategy for patients with CXPA.

## Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

## Authors' Contributions

Xiaoqin Liu, Xiaoyan Liao and Dongwei Zhang contributed to the design and implementation of the study, the analysis of the results and the writing of the article.

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