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Case Report

# Pleomorphic Adenoma with Extensive Mucinous Metaplasia Mimicking Mucoepidermoid Carcinoma: A Case Report and Literature Review

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## Abstract

Pleomorphic adenoma is the most common benign tumor of the salivary glands. Histologically, it is characterized by the presence of both epithelial and mesenchymal elements and may contain various metaplastic changes. This paper reports a case of pleomorphic adenoma with extensive mucinous metaplasia, which is histologically very similar to mucoepidermoid carcinoma. Pleomorphic adenoma with extensive mucinous and squamous differentiation may be misdiagnosed as mucoepidermoid carcinoma. Immunohistochemistry was ineffective in differential diagnosis, and the diagnosis was confirmed by the absence of mastermind like transcriptional coactivator 2 translocation.

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## Introduction

Pleomorphic adenoma (PA) is the most common salivary gland tumor, characterized by biphasic neoplastic proliferation of epithelial and myoepithelial cells. It may contain various metaplastic myoepithelial components that justify its name pleomorphic. Squamous, mucinous, sebaceous, oncocytic, osteogenic, and chondroid metaplasia are the most common.[1,2]

In addition to the production of chondromyxoid stroma, myoepithelial cells are partly responsible for these metaplastic morphological diversities. These morphological variations of PA may be similar to those of other benign and malignant salivary gland tumors, leading to challenges in differential diagnosis.[1–3] On the other hand, various types of malignant salivary gland tumors may arise from PA.[4] These malignant tumors are usually high-grade and show invasive growth.[4] Definitive diagnosis is important in terms of the type of treatment and patient management. For this purpose, genetic studies have also been used for diagnosis.

The presence of extensive mucinous and squamous metaplasia, associated with a cystic change in PA, may cause an appearance that is very similar to mucoepidermoid carcinoma (MEC). In this report, we present a case of PA with intracapsular cystic changes, extensive mucin extravasation, mucinous and squamous metaplasia, which was very similar to MEC.

## Case report

A 27-year-old female patient was admitted to another hospital with the complaint of painless swelling behind the right ear that she had noticed for 1 year. A computer tomography scan performed in this hospital revealed a well-circumscribed mass measuring 4.5x2 cm, located in the right parotid gland, with mild and homogeneous contrast enhancement. After a fine needle aspiration biopsy (FNAB) revealed a salivary gland neoplasm of uncertain malignant potential (SUMP) (Milan category IVB), the patient was referred to our hospital for right parotidectomy.

Grossly, the parotidectomy specimen was 4.5 × 2.5 × 2 cm in size. The cut surface showed a well-circumscribed, cystic, and gelatinous mass 2.5 cm in diameter. The surgical borders of the specimen were intact.

Histological examination showed an encapsulated tumor with extensive mucinous areas (Fig. 1). The cystic areas were often lined by flat epithelium and denuded areas filled with extravasated mucin. No prominent myoepithelium layer was observed in these areas, and there was no myxo-chondroid matrix. There was an intermediate squamous epithelium-like layer under the cystic epithelium in some parts of the tumor. There were also some small squamous epithelial-lined cysts filled with keratin (Fig. 1a). Mucinous cystic areas were not discrete components and showed continuity with small tubules within the hyalinized stroma resembling PA in the subcapsular area (Fig. 1b). Well-differentiated MEC and cystic degenerate pleomorphic adenoma were primarily considered in the histologic differential diagnosis.

Immunohistochemically, there was diffuse and strong cytokeratin 7 immunoreactivity in the lining epithelial cells. There was weak positivity for P63 and calponin antibodies at the periphery of the cystic mucinous and squamoid epithelium (Fig. 2). No staining was obtained with smooth muscle

**Keywords:** Pleomorphic adenoma; Mucinous metaplasia; Squamous metaplasia; Mucoepidermoid carcinoma.

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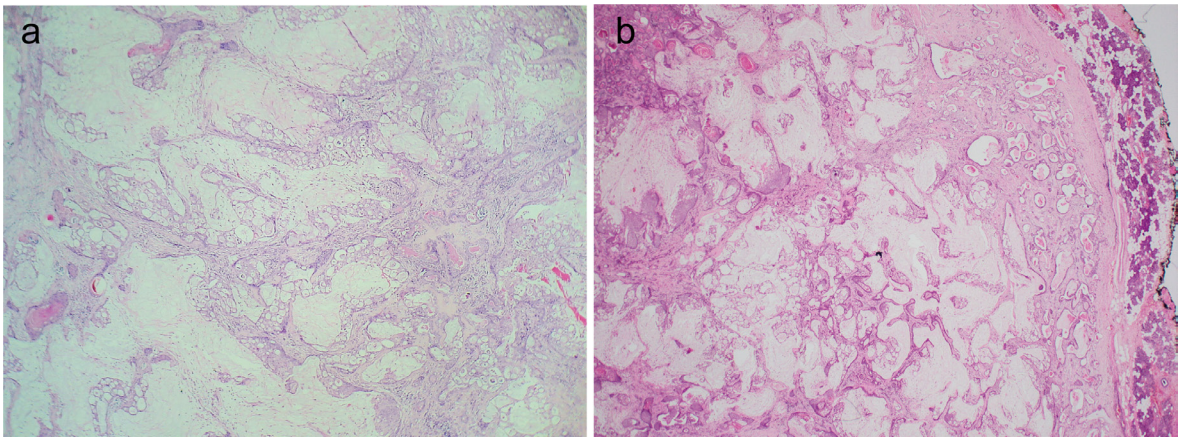


**Fig. 1. Histopathological examination of parotidectomy material.** (a) Mucin-filled cystic tumor lined by mucinous and squamoid cells closely mimicking mucoepidermoid carcinoma (HE, ×40). (b) The encapsulated cystic tumor has small tubules within the hyalinized stroma in the subcapsular area (right). There are keratin-filled squamous epithelial islands (left upper part) (HE, ×10). HE, hematoxylin and eosin stain.

actin or S-100 antibodies. Additionally, Ki-67 immunoreactivity was less than 2%.

Since most low-grade MECs may harbor gene fusions involving mastermind like transcriptional coactivator 2 (MAML2) translocation, fluorescence in situ hybridization (FISH) was performed on formalin-fixed paraffin-embedded section using a commercially available MAML2 dual-color break-apart probe (Z-2014-200, Zytovision, Germany) and FISH-tissue implementation kit (Zytovision, Germany). At least 50 randomly selected nonoverlapping tumor cell nuclei were evaluated for the presence of yellow (normal) or green and red (break apart) fluorescent signals at x400 magnification. Break-apart FISH signaling was negative for the MAML2 rearrangement (50 cells, 0%). This finding supported the diagnosis of PA.

## Discussion

There are numerous morphological variations in myoepithe-

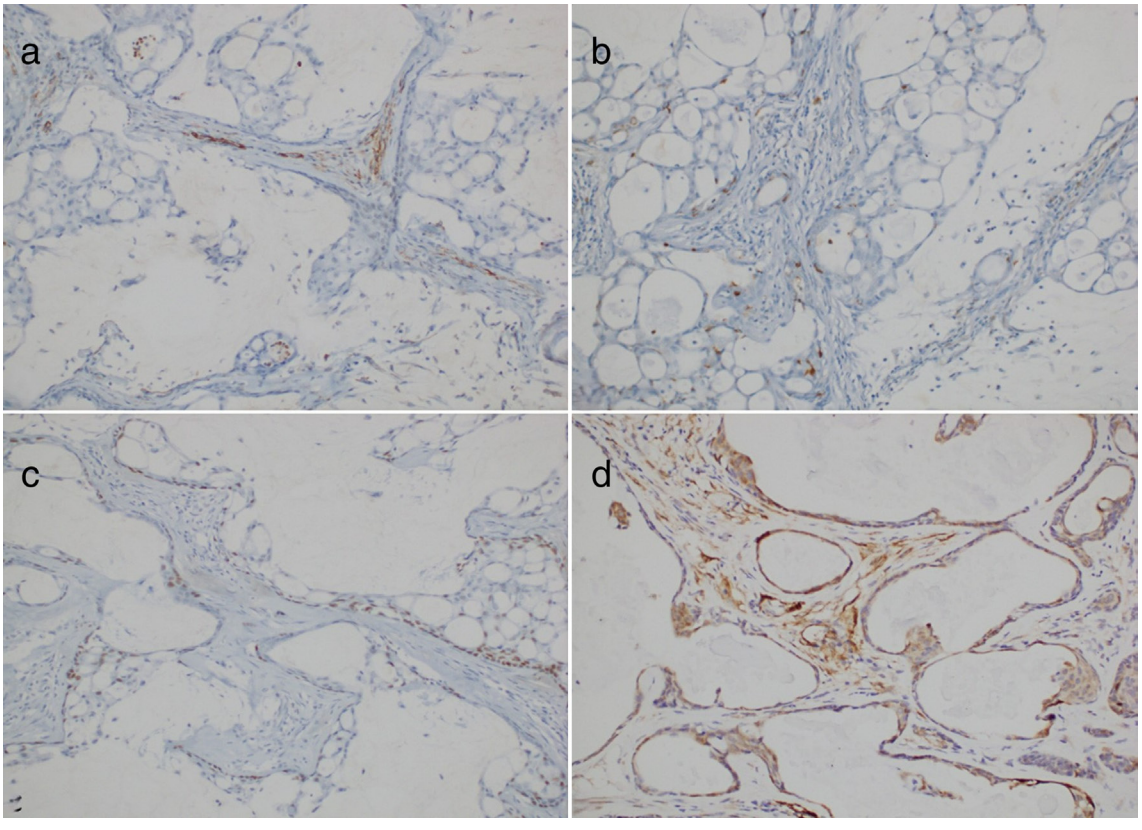


**Fig. 2. Immunohistochemical examination of parotidectomy material.** (a) Immunohistochemical staining revealed SMA and (b) S-100 protein staining. (c) There was weak positivity for P63 and (d) calponin antibodies (avidin-biotin immunohistochemistry, ×200). SMA: smooth muscle actin.

**Table 1. The list of the cases reviewed for metaplasia in pleomorphic adenomas**

| References | Location of Lesion | Number of case | FNAB/FNA/Frozen Diagnosis | Metaplasia | Histopathological Diagnosis |
|---|---|---|---|---|---|
| Brisebois *et al*.[8] | Minor salivary gland | 1 | Squamous cell carcinoma | Squamous | Pleomorphic adenoma |
| Singh *et al*.[7] | Minor salivary gland | 1 | Low Grade Mucoepidermoid Carcinoma | Squamous Adipocytic | Pleomorphic adenoma |
| Hamilton *et al*.[6] | Parotid gland | 1 | Non-neoplastic | Squamous Mucinous | Pleomorphic adenoma |
| Goulard *et al*.[9] | Minor salivary gland | 1 | None | Squamous | Pleomorphic adenoma |
| Joseph *et al*.[10] | Parotid gland | 2 | Pleomorphic adenoma | Squamous | Mucoepidermoid carcinoma |
| Siddiqui *et al*.[11] | Parotid gland | 1 | Pleomorphic adenoma | Adnexa-like | Pleomorphic adenoma |
| Batrani *et al*.[12] | Right minor salivary gland | 1 | Mucoepidermoid carcinoma | Squamous appendageal | Pleomorphic adenoma |
| Guo *et al*.[1] | Parotid and submandibular gland | 4 | None | Squamous Mucinous | Pleomorphic adenoma |
| Hamdan *et al*.[13] | Parotid gland | 1 | Mucoepidermoid carcinoma | Squamous Mucinous | Pleomorphic adenoma |
| Zhu *et al*.[14] | Parotid gland | 2 | None | Mucinous | Pleomorphic adenoma |

FNAB/FNA, fine-needle aspiration biopsy.

lial cells in PA and immunohistochemistry is considered the best method for identifying these cells. However, immunohistochemical stainings may not be completely convincing for myoepithelial differentiation, as in our case.

The encapsulation and keratinization of the glob corne and the presence of small tubules in the peripheral zone of the tumor support the possibility of PA. On the other hand, there was no diagnostic chondromyxoid matrix. Extensive cystic changes, mucus production, the presence of mucous and squamoid cells, and the immunohistochemical absence of convincing myoepithelial differentiation suggest the possibility of MEC.

Guo *et al.* suggested that metaplastic changes resembling MEC can be found in the PA.[1] They do not form a discrete expansile mass but rather merge imperceptibly with the typical PA.[1] The absence of capsular invasion and the presence of keratinization within the lesion also support the diagnosis of PA.[1]

Skalova *et al.* reported that PA may contain large areas of squamous and mucinous metaplasia suspicious of MEC.[2] In contrast to MEC, metaplastic PA does not harbor the distinctive translocations t(11;19) and t(11;15).[2] Metaplastic changes in PA may be diagnostically challenging and cause pitfalls in the diagnosis of fine needle aspirations particularly in the absence of chondromyxoid stroma.[3,5,6] The potential misinterpretations of malignancy are made, especially for MEC.[5] Brachtel *et al.* reported that misinterpretation may lead to over-treatment.[5] On the other hand, MEC may develop as a component of carcinoma ex PA. These tumors are often high-grade and invasive.[4]

In the literature we have accessed in the last 20 years, we have compiled Table 1 summarizing case reports that raise suspicion of malignant salivary gland tumors due to widespread metaplastic changes in the PA.[1,6-14] In this case, a prior FNAB performed elsewhere prompted the excision of the lesion. While evaluating fine needle aspiration biopsies of pleomorphic adenomas can be challenging due to their diverse metaplastic components, the Milan reporting system may place such aspirates in risk categories (III, IVA, IVB, V, or even VI). Therefore, when performing FNAB on these tumors, preparing a cell block is crucial. This allows for the definitive demonstration of myoepithelial differentiation within tumor sections, aiding in diagnosis, and can also be used to confirm the absence of MAML2 translocation.

## Conclusions

In the present case, intracapsular cystic changes, widespread mucin extravasation, the absence of myxochondroid matrix, and the formation of an intermediate squamous epithelium-like layer under the cystic epithelium in some parts of the tumor caused problems in the differential diagnosis in terms of histomorphology. Immunohistochemistry is considered the best method for identifying myoepithelial cells. However, in our case, it was observed that immunohistochemical staining did not fully support myoepithelial differentiation.

It is known that many well-differentiated MECs can harbor gene fusions involving the MAML2 translocation. Our case was negative for MAML2 rearrangement (50 cells, 0%). The absence of MAML2 translocation supported the definitive diagnosis of PA. Evaluation of molecular test results, as in our case, guides the suitability of treatments and follow-up. Definitive diagnosis is crucial as it significantly impacts treatment and patient management.

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## Conflict of interest

The authors declared no potential conflicts of interest with

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## Author contributions

Collected the clinical data and wrote the manuscript (ÇS), made histological, immunohistochemical examination and FISH analysis (ÖB), made the final diagnosis of this disease (ÖG). All authors have made a significant contribution to this study and have approved the final manuscript.

## Ethical statement

This single case report of clinical cases was a retrospective analysis of three or fewer clinical cases and is not considered human research according to the TOBB ETU Hospital institutional review board (IRB) regulations. IRB approval was thus deemed unnecessary. This study was performed in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

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