

# Polymorphous Adenocarcinoma – A rare presentation with emphasis on Immunohistochemical profile

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## ABSTRACT

**Introduction:** Polymorphous Adenocarcinoma is a rare asymptomatic slow growing malignant salivary gland tumor with infiltrative growth, multiple architectural growth patterns and cellular uniformity. Intraorally palate is the preferred location followed by upper lip, buccal mucosa, posterior tongue and retromolar trigone.

**Case Presentation:** A case of Polymorphous adenocarcinoma with an unusual clinical as well as histological picture is presented here along with an attempt to throw a light on its immunohistochemical profile.

**Conclusion:** Our study thus emphasises the need for thorough clinical and histopathological examination along with immunohistochemistry for the proper diagnosis and timely management.

**Keywords:** Galectin 3, Immunohistochemistry, Polymorphous Adenocarcinoma

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## INTRODUCTION

Polymorphous Adenocarcinoma (PAC) also called as terminal duct carcinoma, lobular carcinoma or low grade papillary adenocarcinoma is a rare asymptomatic slow growing malignant salivary gland tumor with infiltrative growth, multiple architectural growth patterns and cellular uniformity. It was earlier termed Polymorphous Low Grade Adenocarcinoma, first used in 1984 by Evans and Batsakis<sup>1</sup> to describe this tumor entity which was thought to be originated from the progenitor cells of distal/ terminal duct portions of the salivary gland unit. Update on salivary gland tumors in the 4th edition of WHO classification of Head and Neck tumors in 2017, the term low grade was dropped and the tumor was entitled PAC; as the architectural variations in this tumor showed a difference in its aggressiveness and biologic behaviour which raised the question of whether these tumors are always low grade. Herewith we report a case of PAC in a 65 year old man in the anterior maxillary gingiva highlighting the challenges encountered in diagnosis which was later confirmed by immunohistochemistry.

## CASE REPORT

A 65 year old man reported to the Department of Oral and Maxillofacial Surgery with the complaint of a growth in the maxillary anterior right side gingival region. Medical, dental and family history were not relevant. All the vital and peripheral signs were within normal limits. No relevant findings on extraoral examination and on intraoral examination, it revealed a proliferative growth of size approximately 2.5 x 2.0 cm on the labial gingival aspect of 11,12,13 extending to the mucobuccal sulcus which was firm and non tender. There was no palpable lymph nodes. On the basis of clinical examination, a provisional diagnosis of reactive hyperplasia was given. Because of the location of the lesion, peripheral odontogenic tumor was also considered.

Orthopantomograph showed a widening of the periodontal

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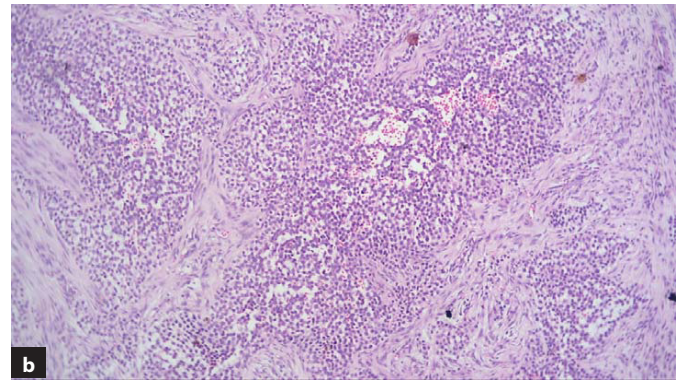
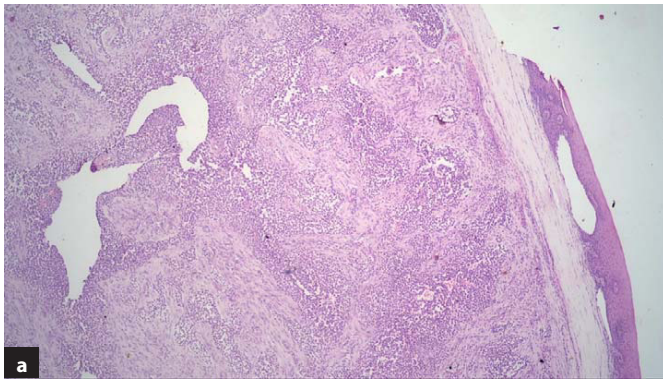
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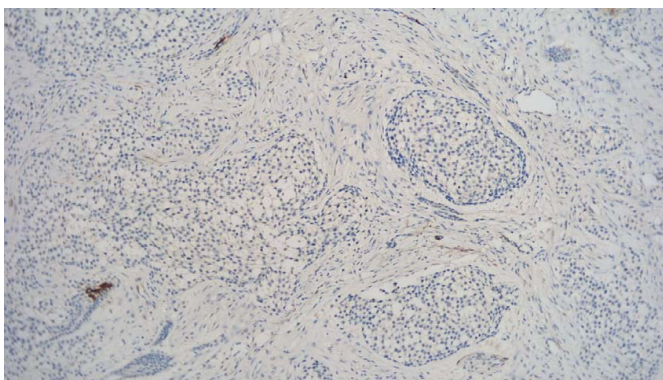
**Conflict of Interest:** None

ligament space and loss of lamina dura of 11, 12, 13 and 21, 22, 23. All the haematological parameters were within the normal range. Histopathologic section of the lesion showed stratified squamous epithelium which is separated from the underlying neoplastic mass by a thick fibrous capsule. The neoplastic cells were round to ovoid with hyperchromatic nuclei and scant cytoplasm, with intervening microcystic areas arranged in lobules. These lobules were separated by a fibrous collagenous stroma. The cells showed nuclei with fine chromatin and inconspicuous nucleoli and a few cells showed clearing of cytoplasm. Scant mitosis, but no necrosis or perineural invasion was seen. [Figure 1a and 1b]. Based on these findings a differential diagnosis of odontogenic neoplasm or minor salivary gland neoplasm was made. A definite diagnosis could be made only after confirmation with immunohistochemistry which included CK7, CK19, calponin and Galectin-3. CK7, CK19 and calponin were negative [Figure 2, 3 and 4 respectively] and Galectin-3 showed a strong cytoplasmic positivity [Figure 5] which paved the way to a final diagnosis of Polymorphous Adenocarcinoma.

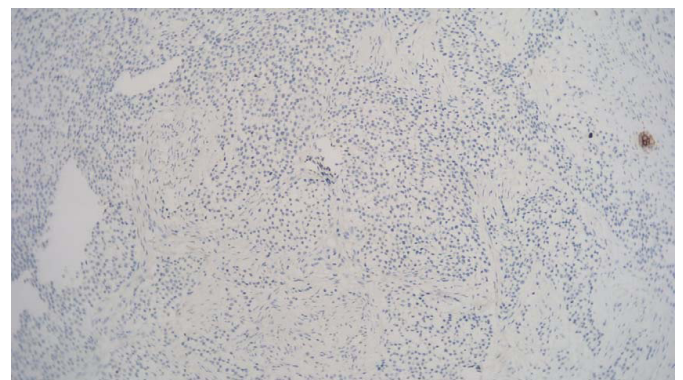




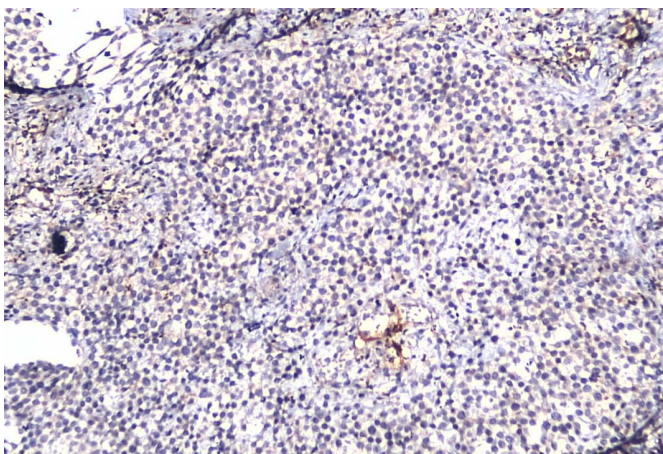
**Fig 1** a) Stratified squamous epithelium which is separated from the underlying neoplastic mass by a thick fibrous capsule; H & E 4x  
b) The neoplastic cells were round to ovoid with hyperchromatic nuclei and scant cytoplasm, with intervening microcystic areas arranged in lobules. Lobules were separated by a fibrous collagenous stroma. H & E 10x



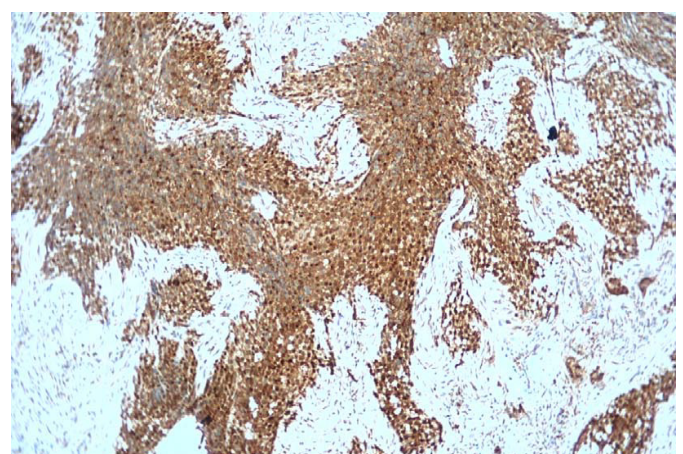
**Fig 2:** Negative immunohistochemical staining with CK7; 10x



**Fig 3:** Negative immunohistochemical staining with CK19; 10x



**Fig 4:** Negative immunohistochemical staining with calponin; 10x



**Fig 5:** Immunohistochemical staining with Galectin 3 showing cytoplasmic positivity in tumor cells, 10x

## DISCUSSION

Polymorphous Adenocarcinoma is a rare tumor that mostly affects minor salivary glands of the oral cavity, however recently there have been reports with its presentation in major salivary glands<sup>2</sup>, the breast<sup>3</sup>, paranasal sinuses<sup>4</sup>, the skin and orbit<sup>5</sup>, vulva and vagina<sup>6</sup>. Primary<sup>7,8</sup> as well as metastatic<sup>9,10</sup> lung lesions have also been reported. Intraorally palate is the preferred location with reported incidences between 45%<sup>2</sup> and 78%<sup>11</sup> but other intraoral sites in-

clude the upper lip, buccal mucosa, posterior tongue and retro-molar trigone. To the best of our knowledge, this is the first case reported in the anterior maxillary labial gingival region. Two cases were reported in the lower lip<sup>12,13</sup>. The age of incidence is usually in the sixth to seventh decades of life but rare occurrences in adolescents have been reported<sup>14,15,10</sup>. In accordance with the literature, our patient was in the seventh decade of life. It is reputed as the 2nd most common malignancy of the minor salivary gland follow-



ing mucoepidermoid carcinoma<sup>16</sup> which usually shows a female gender predilection in the ratio of 2-4.6:1<sup>17</sup>. Our case in the contrary was in a male patient.

Although the lesion has a locally infiltrative growth pattern and perineural and perivascular invasive characteristics, PAC is generally known to be clinically innocuous<sup>3,18</sup>. It was considered to be of low grade malignant potential with nodal metastasis seen only in a minority of case and distant spread occurring in less than 1% of cases<sup>10,19</sup>. However there have been few cases where the lesion is locally aggressive<sup>10,19,20</sup>. Inadequate excision with positive margin, repeated surgery, exposure to radiation, prolonged duration and occurrence in a young patient are the factors which contribute to an aggressive clinical progression of the lesion<sup>10,19,21</sup>. These developments along with the interesting observation in the literature that the potential for histological transformation of the lesion from a low grade to a high grade malignancy<sup>10,19</sup> led to the emergence of the term Polymorphous Adenocarcinoma by dropping 'low grade' from the earlier name of the lesion.

Besides the invasive growth pattern, PAC is characterised by morphological diversity and cytological uniformity. The highly variable growth patterns include tubular, solid, papillary, microcystic, cribriform, fascicular, single file and strand like arrangements<sup>19,20</sup>. The present case showed neoplastic cells which are stellate, spindle, polygonal cells with eosinophilic and clear cytoplasm and round to oval nuclei, fine chromatin and inconspicuous nucleoli arranged in lobules which are separated by a fibrous collagenous stroma. Scant mitosis was seen although the literature accounts for an average mitotic count of only 1/10 HPF with atypical mitosis as not a feature of PAC<sup>22</sup>. Necrosis was not seen which is in accordance with that in literature<sup>23</sup>. Perineural invasion or neurotropism considered to be a characteristic feature of PAC was not evident in the present case. Diagnostic difficulties however arise in needle or incisional biopsies where the periphery of the tumor is not available to determine whether infiltrative growth is present or absent.

Diagnostic difficulties due to histopathologic overlap occur with Adenoid Cystic Carcinoma (ACC). The histologic appearance in the present case suggested Clear cell Odontogenic Carcinoma and Clear cell Myoepithelial Carcinoma to be considered as differential diagnosis. ACC and PAC may share histologic features as infiltrating solid, tubular and cribriform patterns, presence of cystic spaces and neurotropism<sup>24</sup>. The importance of its distinction however lies in much more indolent behaviour of PAC compared to ACC. Immunohistochemistry may be indicated for this type of diagnostically challenging histopathologic lesion.

Galectin 3 is a 31 kDa member of  $\beta$ -galactoside binding animal lectin family<sup>25</sup>. This multifunctional protein is expressed in normal as well as tumoral cells mainly found in the cytoplasm, although depending on the cell type and proliferative state; it can also be detected in the nucleus or the cell surface or in the extracellular environment<sup>26,27,28</sup>. It also plays its role in biological events like angiogenesis, cell adhesion, proliferation, differentiation<sup>29</sup>; also in tumor progression, cellular transformation and metastases<sup>30,31,32,33</sup>. Studies have shown the role of Galectin-3 in differentiating PAC from ACC<sup>34</sup>. As with our case Galectin-3 shows cytoplasmic reaction of all the neoplastic cells in PAC while in ACC only the luminal cells stain positively to Galectin-3 that too in the nuclei.

Metastatic lesions to the oral cavity if it targets the soft tissue, attached gingiva with a preference to the maxillary gingiva in a clinical presentation resembling reactive lesion or pyogenic granuloma is seen. As the present case very well satisfies this presentation

the possibility of metastatic lesion had to be ruled out. Cytokeratin 7 (CK7) is a type II keratin of simple nonkeratinizing epithelia with a molecular weight of 51.4 kDa. Adenocarcinomas of the lung<sup>35</sup>, pancreas, small intestine and renal cell carcinomas have been reported to be CK7 positive which was negative for the present case.

Furthermore, C19 and calponin were negative for the present case which ruled out the possibility for an odontogenic and myoepithelial origin of the lesion.

Recurrence as well as metastases from PAC are rare; as estimated from reports, as a whole PAC show local recurrence rates of 10-33% and regional metastases in 9-15%<sup>36</sup>. The present case emphasizes the need for thorough clinical, radiographical and histopathological examination with immunohistochemical profile for the proper diagnosis and timely management of the lesion to prevent local recurrences and distant metastasis.

## REFERENCES

- Evans HL, Batsakis JG (1984) Polymorphous low-grade adenocarcinoma of minor salivary glands. A study of 14 cases of distinctive neoplasm. *Cancer* 53:935-942
- Yih WY, Kratochvil FJ, Stewart JC (2005) Intraoral minor salivary gland neoplasms: review of 213 cases. *J Oral Maxillofac Surg* 63:805-810
- Asioli S, Marucci G, Ficarra G et al (2006) Polymorphous adenocarcinoma of the breast. Report of three cases. *Virchows Arch* 448:29-34
- Charous DD, Cunnane MF, Rosen MR et al (2005) Recurrent polymorphous low-grade adenocarcinoma manifesting as a sinonasal mass: a case report. *Ear Nose Throat J* 84:354-357
- Thomas KM, Cumberworth VL, McEwan J (1995) Orbital and skin metastasis in polymorphous low-grade adenocarcinoma of the salivary gland. *J Laryngol Otol* 109:1222-1225
- Young S, Leon M, Talermin A et al (2003) Polymorphous lowgrade adenocarcinoma of the vulva and vagina: a tumor resembling adenoid cystic carcinoma. *Int J Surg Pathol* 11:43-49
- Lee VK, McCaughan BC, Scolyer RA (2004) Polymorphous lowgrade adenocarcinoma in the lung: a case report. *Int J Surg Pathol* 12:287-292
- Kyu Do Cho, Ji Han Jung, Deog Gon Cho et al (2007) Primary polymorphous low grade adenocarcinoma of lung treated by sleeve bronchial resection: a case report. *J Korean Med Sci* 22:373-376
- Hannen EJ et al (2000) Polymorphous lowgrade adenocarcinoma with distant metastases and deletions on chromosome 6q23-qter and 11q23-qter: a case report. *J Clin Pathol* 53:942-945
- Tanaka F, Wada H, Inui K et al (1995) Pulmonary metastasis of polymorphous low-grade adenocarcinoma of the minor salivary gland. *Thorac Cardiovasc Surg* 43:178-180
- Buchner A, Merrell PW, Carpenter WM. Relative frequency of intra-oral minor salivary gland tumors: a study of 380 cases from northern California and comparison to reports from other parts of the world. *J Oral Pathol Med* 2007; 36:207-214.
- Chaabouni S, Ayadi L, Dhoubi H et al (2008) Polymorphous lowgrade adenocarcinoma: a palatine and a labial location. *Rev Stomatol Chir Maxillofac* 109:178-182
- A. A. Olusanya, O. A. Akadiri, V. I. Akinmoladun, B. F. Adeyemi. Polymorphous Low Grade Adenocarcinoma: Literature Review and Report of Lower Lip Lesion with Suspected Lung Metastasis. *J. Maxillofac. Oral Surg.* (Jan-Mar 2011) 10(1):60-63
- Lee VK, McCaughan BC, Scolyer RA (2004) Polymorphous lowgrade adenocarcinoma in the lung: a case report. *Int J Surg Pathol* 12:287-292
- Lengyel E, Somogyi A, Godney M et al (2000) Polymorphous low-grade adenocarcinoma of the nasopharynx. Case report and review of literature. *Strahlenther Onkol* 176:40-42
- Waldron CA, el-Mofty SK, Gnepp DR (1988) Tumors of the intraoral minor salivary glands: a demographic and histologic study of 426 cases. *Oral Surg Oral Med Oral Pathol.* 66:323-333
- Toida M, Shimokawa K, Makita H et al (2005) Intra oral minor salivary gland tumours: a clinicopathological study of 82 cases. *Int J Oral Maxillofac Surg* 34:528-532

18. Vincent SD, Hammond HL, Finkelstein MW (1994) Clinical and therapeutic features of polymorphous low-grade adenocarcinoma. *Oral Surg Oral Med Oral Pathol* 77:41–47
19. Simpson RH, Pereira EM, Ribeiro AC et al (2002) Polymorphous low grade adenocarcinoma of the salivary glands with transformation to high-grade carcinoma. *Histopathology* 41:250–259
20. Harry L, Evans MD, Mario A et al (2000) Polymorphous lowgrade adenocarcinoma a study of 40 cases with long-term follow up and an evaluation of the importance of papillary areas. *Am J Surg Pathol* 24:1319–1328
21. Pelkey TJ, Mills SE (1999) Histologic transformation of polymorphous low-grade adenocarcinoma of salivary gland. *Am J Clin Pathol* 111:785–791
22. Perez-Ordóñez B. Selected topics in salivary gland pathology. *Curr Diagn Pathol* 2003;9:355–65.
23. Zarbo RJ. Salivary gland neoplasia: A review for the practicing pathologist. *Mod Pathol* 2002;15:298–323.
24. Barnes L, Everson JW, Reichart P, Sidransky D. World healthy organization classification of tumours. Pathology and genetics of head and neck tumours. Lyon: IARC Press; 2005., p. 221–4 chapter 5.
25. Barondes SH, Cooper DNW, Gitt MA, Leffler H. Galectins: structure and function of a large family of animal lectins. *J Biol Chem* 1994;269:20807–10.
26. Kasai K, Hirabayashi J. Galectins: a family of animal lectins. *J Biochem* 1996;119:1–8.
27. Hughes RC. Secretion of the galectin family of mammalian carbohydrate-binding proteins. *Biochem Biophys Acta* 1999; 1473:172–85.
28. Davidson PJ, Davis MJ, Patterson RJ, Ripoché MA, Poirier F, Wang JL. Shuttling of galectin-3 between the nucleus and cytoplasm. *Glycobiology* 2002;12(5):329–37.
29. Dumic J, Dabelic S, Flo“gel M. Galectin-3: an open-ended story. *Biochim Biophys Acta* 2006;1760(4):616–35.
30. Ellerhorst J et al. Galectin-1 and galectin-3 expression in human prostate tissue and prostate cancer. *Urol Res* 1999;27(5):362–7.
31. Pacis RA et al. Decreased galectin-3 expression in prostate cancer. *Prostate* 2000;44:118–23.
32. Nakamura M et al. Involvement of galectin-3 expression in colorectal cancer progression and metastasis. *Int J Oncol* 1999;15(1): 143–8.
33. Takenaka Y et al. Galectin-3 and metastasis. *Glycoconj J* 2004;19:543–9.
34. K.L. Ferrazzo et al. Galectin-3 immunoprofile in adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma of salivary glands *Oral Oncology* (2007) 43, 580–585
35. Gurda GT et al. Utility of five commonly used immunohistochemical markers TTF-1, Napsin A, CK7, CK5/6 and P63 in primary and metastatic adenocarcinoma and squamous cell carcinoma of the lung: a retrospective study of 246 fine needle aspiration cases. *Clin Transl Med.* 2015;4(1). doi:10.1186/s40169-015-0057-2
36. R. R. Seethala, G. Stenman. Update from the 4th Edition of the World Health Organization Classification of Head and Neck Tumours: Tumours of the Salivary Gland. *Head and Neck Pathol* (2017) 11:55–67

#### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.