Case Report

Polymorphous adenocarcinoma: A case report along with its characteristics and diagnostic challenges

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Abstract

Polymorphous adenocarcinoma (PAC) is an uncommon tumor that affects minor salivary glands mainly. It presents as an indolent malignancy that frequently manifests as an asymptomatic, slow-growing mass within the oral cavity, especially palate and its clinical behavior resembles that of benign neoplasm, often causing delay in the diagnosis. Here, we report a rare case of PAC of palate in a 49-year-old female patient along with a concise review of characteristics of PAC and highlight diagnostic challenges caused by the overlap of clinical and microscopic features between PAC, pleomorphic adenoma and adenoid cystic carcinoma.

Keywords: Adenocarcinoma, differential, palate, polymorphous, salivary glands

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INTRODUCTION

Polymorphous adenocarcinoma (PAC) is a rarely encountered salivary gland neoplasm, with an almost exclusive propensity to arise from minor salivary glands. PAC is characterized by most striking features of its appearance, an infiltrative growth pattern and low metastatic potential.[1] PAC has become a challenging entity for the clinicians to diagnose because of overlap of its clinical and microscopic features with other salivary gland tumors mainly pleomorphic adenoma (PA) and adenoid cystic carcinoma (Ad CC).[2] Here, we present a case report of PAC occurring in palate region of a 49-year-old female along with differential diagnosis of this tumor.

CASE REPORT

A 49-year-old female reported with painless swelling on the left side of maxilla in the palatal region from the past 4–5 months. The patient had visited local practitioner for the treatment. Doctor treated with incision, drainage and antibiotics. However, patient had no relief and the swelling continued to increase. Later, she reported to our institute. Intra-oral examination showed the presence of round-to-oval swelling in left maxilla at the junction of hard and soft palate [Figure 1a]. It was firm, nontender with central ulceration. The patient had given no relevant medical history.

Based on clinical findings, provisional clinical diagnosis of minor salivary gland tumor was made.

An excisional biopsy [Figure 1b] was performed under LA, and a bony crater-like defect was seen on the palatal bone near the greater palatine foramen after soft-tissue removal. Histopathological examination revealed an intact

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stratified epithelium overlying the tumor mass [Figure 2a] with infiltrative margins at few foci. At the tumor periphery, cells were arranged in "Indian file" or "beads on a string" pattern of infiltration [Figure 2b]. Tumor cells showed polymorphous architecture including solid, tubular, glandular, cribriform and ductal patterns [Figure 3a-c]. The ducts were lined by a single layer of cuboidal cells. Cells were round to polyhedral, isomorphic with pale oval nuclei "washed out" chromatin [Figure 4a], inconspicuous nucleoli, no evidence of mitosis. The cells had a thin rim of lightly eosinophilic cytoplasm with indistinct borders. Ductal lumina contained periodic acid-schiff positive mucin that was weakly mucicarmine positive [Figure 4b]. Intracytoplasmic mucicarmine positivity was typically absent [Figure 4c]. The tumor stroma was composed of fibrous tissue with varying degrees of hyalinization and slate gray blue myxoid change [Figure 5a]. Concentric whirling around neurovascular bundles producing a targetoid appearance was also seen [Figure 5b]. On microscopic examination, there was a conflict of opinion over the distinction between PAC, PA and AdCC. Immunohistochemical (IHC) investigations were performed to resolve the issue which revealed that the tumor cells showed intense immunopositive staining for CK 7/Vimentin/S-100, focal immune reactivity with P63 and Weak immunoexpression of CD117 (c-kit) [Figure 6].

A final diagnosis of PAC was accorded based on the clinical, histopathologic and IHC investigations. The patient was referred to an oncologist for further management. Partial maxillectomy was done with the closure of palatal surgical defect by maxillary obturator. No sign of recurrence was observed in following 1-year postsurgery. After the

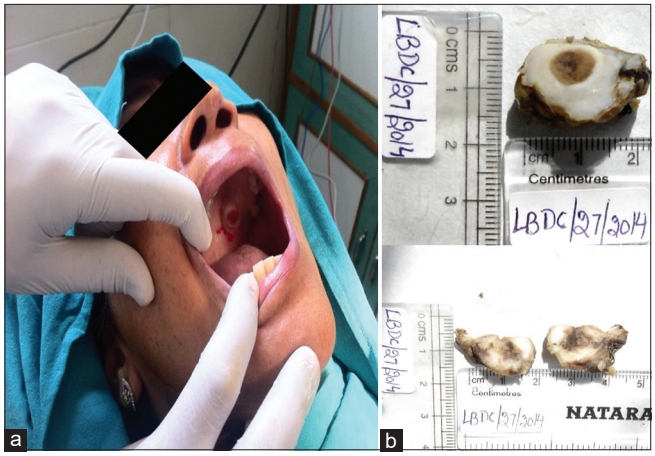

Figure 1: (a) Clinical photograph showing intraoral solitary, well-defined, dome-shaped swelling on the left postero-lateral part of the palate. (b) Photograph of gross specimen

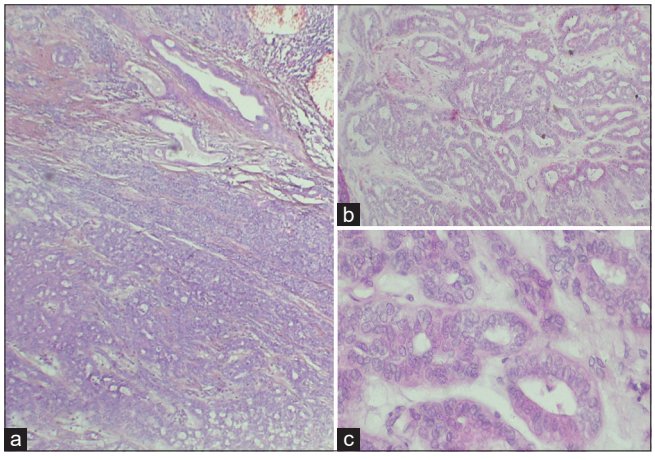

Figure 3: (a) Polymorphous adenocarcinoma tumor cells arranged in combination of solid and tubular pattern (H&E, ×40), (b) cribriform, pseudo adenoid cystic pattern (H&E, ×100), (c) Areas with well-formed tubules (H&E, ×400)

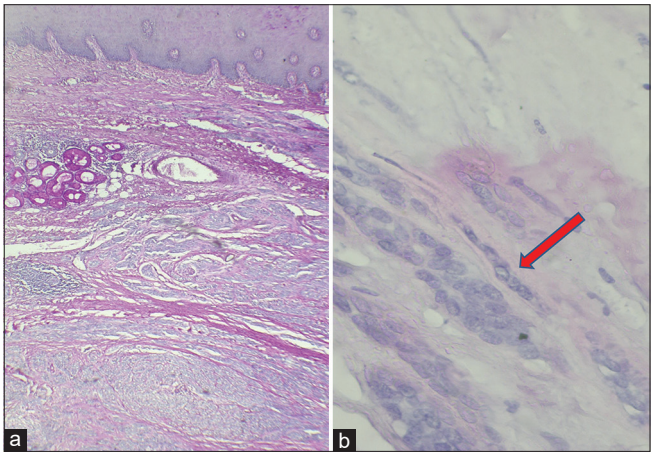

Figure 2: (a) The oral stratified squamous Para keratinized epithelium is seen overlying the uncapsulated tumor growth. Residual minor salivary gland tissue is seen surrounded by tumor islands; although it is not infiltrated directly (H&E, ×40) (b) "Indian file" (arrow) cellular arrangement at tumor periphery (H&E, ×400)

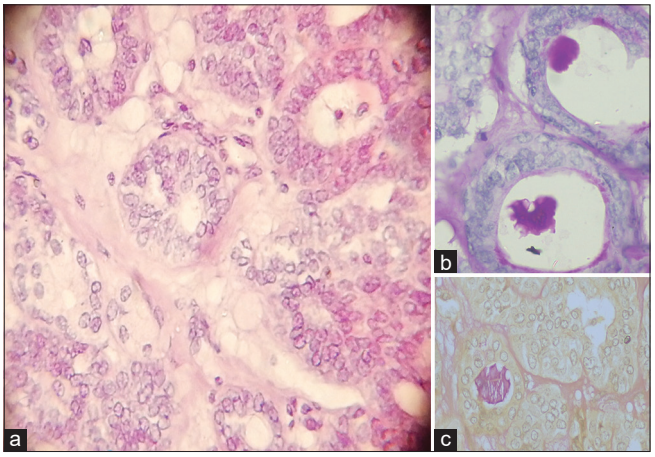

Figure 4: (a) Photomicrograph show cytologically bland glandular islands with uniform, bland vesicular "open" nuclei with inconspicuous nucleoli (H&E, ×400), (b) The ductal elements appeared to be lined by a single layer of cuboidal cells and Lumina contains periodic acid schiff positive mucin (H&E, ×400), (c) Intracytoplasmic mucicarmine positivity typically absent along with weakly positive luminal mucin (H&E, ×400)

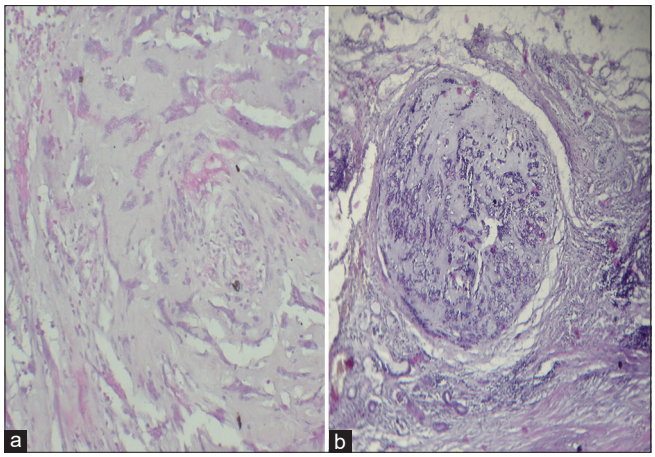

Figure 5: (a) Slate gray-blue myxoid change in the background stroma (H&E, ×100), (b) Concentric whirling around neurovascular bundles producing a targetoid appearance (H&E, ×100)

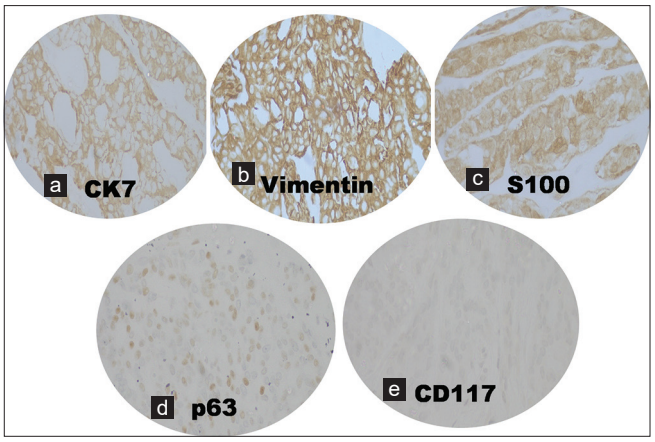

Figure 6: Polymorphous adenocarcinoma tumor cells with strong diffuse positivity for (a) CK7 (b) Vimentin (c) S100 (d) p63 (e) tumor cells, negative for CD117

initial 1 year of follow-up, the patient stopped to attend the follow-up clinics and efforts to reach her has been unsuccessful.

DISCUSSION

The tumor was previously known as "low-grade papillary adenocarcinoma," "lobular carcinoma," "terminal duct carcinoma" and "Polymorphous low-grade adenocarcinoma." The present terminology, PAC, has been opted by the WHO in 2017 as "a malignant epithelial tumor characterized by cytological uniformity, morphological diversity and an infiltrative growth pattern.[3]

PAC is considered to be the second most common malignancy of minor salivary glands occurring intraorally as reported in various studies. The tumor has a wide range of age involvement with the peak incidence in 6th to 7th decade. It has female predilection with approximately 2:1 female-to-male ratio. PAC occurs exclusively in the minor salivary glands, mostly palate, buccal mucosa or the upper lip.[4] Other sites are tongue, oropharynx, sinonasal region and lungs and major salivary glands mainly parotid.

Palate is considered to be the predominant site of occurrence because of the presence of abundant glandular tissue in this area, especially at the junction of hard and soft palate.[5]

Clinically, PAC manifests as asymptomatic round to oval, firm, solid, slow-growing mass associated with pain, ulceration and bleeding. The tumor may also get fixed to underlying structures. Present case was also reported in a 49-year-old female patient on the palatal region of left maxilla as painless swelling that was firm and ulcerated. This correlates with the similar features of PAC reported in the literature. The patient first noticed the swelling 4–5 months back that increased gradually up to current size.

Since PAC occurs mostly in palatal region, it can be confused with so many other lesions clinically. In the present case, on the basis of clinical features, provisional diagnosis of minor salivary glands tumor was made. The other most common tumors involving the palatal minor salivary glands are PA and AdCC [Table 1].

PA is benign and mainly involves major salivary glands, mostly parotid, yet it bears close resemblance to PAC when it occurs in minor salivary glands. These are age and sex predilection, palatal predilection, asymptomatic, slow growth, firm consistency and smooth texture. The lesion is not ulcerated usually.[6]

AdCC mimics PAC in age distribution, sex predilection, palatal involvement, perineural invasion and slow growth. However, in comparison to PAC, it may be associated with pain and frequent ulceration, more distant metastasis, high recurrence rate, worse prognosis and different line of treatment.[7]

Due to wide overlap of the clinical features of PAC with other minor salivary gland neoplasms, it becomes uncertain to give an exact diagnosis only on the basis of clinical findings. To confirm the final diagnosis, histopathological examination is essential.

Grossly, PAC is firm-to-solid ovoid mass lying in close proximity to the overlying epithelium. It is unencapsulated and well circumscribed. Cut surface is light yellow to tan.

Microscopically, PAC is characterized by unencapsulated, infiltrative borders of bland-looking tumor cells arranged

Table 1: Clinical differential diagnosis of polymorphous adenocarcinoma occurring in minor salivary gland region especially palate

Characteristic	PAC	PA	AdCC
Type	Malignant	Benign	Malignant
Age (decades)	6^{th}-7^{th} (peak), but can occur at any age	3^{th}-5^{th}	5^{th}-7^{th}
Sex	Female	Female	Female
Most common site	Palate	Palate	Palate
Symptoms	Asymptomatic	Asymptomatic	Pain
Perineural invasion	Present	Absent	Present
Growth	Slow	Slow	Slow
Consistency	Firm	Firm	Firm
Ulceration	Not always	Not	Present
Fixity to underlying skin/structures	May be	Present	Present
Distant metastasis	Rare	Rare	Present
Recurrences	Less	More	More
Prognosis	Good	Good	Poor

PAC: Polymorphous adenocarcinoma, PA: Pleomorphic adenoma, AdCC: Adenoid cystic carcinoma,

in diverse architectural patterns. Although PAC is well circumscribed, it is invasive and locally destructive.[8] There is destruction of native seromucinous glands and lobules of glands are incarcerated within the body of the neoplasm. Surface epithelium remains intact but may be ulcerated.[4] In the present case, an intact stratified epithelium overlying the tumor mass with tumor cells arranged in Indian file pattern was seen in the subepithelial region. One of the unique features of PAC is "targetoid appearance" produced by concentric or whirling arrangement of tumor cells around small neurovascular bundle. It was also appreciated in our case. Bone invasion may be seen in large lesions in the hard palate as in the present case bony crater-like defect was seen on the underlying palatal bone.[9]

The striking feature of PAC is its variable growth patterns in a single tumor mass giving rise to its name "polymorphous." Histologically, the tumor is composed of multitude of growth patterns such as solid, glandular, tubular, trabecular, cribriform, linear, papillary, fascicular, microcystic and single cell patterns.[10] Tumor cells form multiple cylindrical cyst such as spaces resembling Swiss cheese or honey comb creating a cribriform pattern mimicking AdCC. A very characteristic finding of PAC is an arrangement of tumor cells in a single layer, especially near the periphery of tumor mass forming "Indian file" or "beads on a string" pattern.[4] In the present case, the predominant patterns seen were solid, tubular, glandular, cribriform, ductal and Indian file pattern. Another hallmark of PAC is the presence of uniform cytological features of tumor cells. The tumor cells are bland, round to polygonal, small to medium size, with indistinct cellular borders, pale to eosinophilic cytoplasm, uniformly round to ovoid nuclei containing open, vesicular, "washed out" chromatin and inconspicuous to small nucleoli and rare mitotic figures. Necrosis is absent. Similar findings were observed in our case too. The tumor is made up of fibrous tissue stroma with varying degrees of myxohyaline change. In the present case also, the tumor mass showed such changes. A characteristic slate gray–blue stroma can also be appreciated.[4]

Despite its striking pathology, PAC remains a challenge to diagnose because some of its microscopic features mimic other salivary gland tumors such as PA and AdCC. In our case also, similar confusion was created after viewing the histopathological sections. Many of features showed close resemblance to microscopic features of PA and AdCC [Table 2].

PA is a benign salivary gland neoplasm characterized by its diverse morphology. Cellular component is made up of ductal and myoepithelial cells dispersed in mucopolysaccharide stroma. PA is well circumscribed but may or may not be encapsulated.[11] However, when PA involves minor salivary glands, it appears to be unencapsulated with infiltrative margins having focal extension into adjacent salivary glands. In that case, it becomes difficult to distinguish it from PAC with similar features. The presence of hyalinized stroma in PAC may be mistaken for the mucoid myxoid matrix of PA. Targetoid and "Indian file" infiltration are the characteristic of PAC and not PA. Chondromyxoid stroma present in PA is not seen in PAC. In PA, ducts are lined by double layer of cells, while in PAC, this lining is single layered.[4]

AdCC can mimic the growth patterns and perineural invasion identified in PAC. Cribriform areas for AdCC are typically rigid, whereas both rigid, reticular. Or "lacy" type, cribriform may be observed in PAC.[5] Tubules are lined by double layer of cells in AdCC, while in PAC, by single cell layer. Cyst formation, calcific deposits and papillary growth pattern reveal the diagnosis of PAC than AdCC.[10] In contrast with PAC, AdCC consists of

Table 2: Microscopic differential diagnosis of polymorphous adenocarcinoma

Characteristics	Polymorphous adenocarcinoma	Pleomorphic adenoma	Adenoid cystic carcinoma
Capsulation	**Absent**	**Variable**	**Absent**
Boundary	Well circumscribed	Well circumscribed	Not well circumscribed
Morphological diversity	Striking feature	Present	Not so diverse
Patterns			
Cribriform	Rigid and patchy	Not so prominent	Major component
Papillary	Present	Rare	Absent
Indian file	Present	Absent	Absent
Ductal lining	Single layered	Double	Double
Targetoid	Characteristic	Absent	Absent
Cells	Epithelioid	Epithelial and myoepithelial	Epithelial and myoepithelial
Nuclei	Homogeneous, pale, vesicular, washed out chromatin	Uniform, pale with granular chromatin	Condensed hyperchromatic
Mitotic activity	Infrequent	Rare	High
Stroma	Variable; hyaline, mucoid to fibrovascular, bluish gray tinge	Variable: hyaline, mucoid, fibrous	Variable-hyaline, chondromyxoid, osseous
Perineural invasion	Present	Absent	Present

heterogenic architecture formed by dimorphic population composed of myoepithelial and epithelial cells. They tend to be smaller, with hyperchromatic nuclei, inconspicuous nucleoli, less cytoplasm, a higher nuclear-to-cytoplasmic ratio and coarser nuclear chromatin in contrast to the cells of PAC, which are isomorphic with moderate amount of eosinophilic cytoplasm and vesicular nuclei with fine chromatin AdCC lacks the slate-gray background matrix and targetoid pattern of PAC. The solid areas of PAC also lack the nuclear pleomorphism, small and angular nuclei, necrosis and mitotic activity that are often seen in the solid variant of AdCC.[10]

The conflict of these overlapping histopathological features can be best resolved by IHC investigations. Till date, no reliable molecular marker could be identified to distinguish PAC from other malignant minor salivary gland tumors. Studies have shown marked expression of Glial fibrillary acid protein (GFAP), in PA; Vimentin, Cytokeratin, S-100, CK-7, muscle specific actin and epithelial membrane antigen in PAC,[12] and Ki67, c-kit (CD117), alpha smooth muscle actin (alpha-MSA), p53, bcl-2 and carcinoembryonic antigen in AdCC.[13] GFAP expression is not evident in PLGA.[14]

In our case, IHC revealed that the tumor cells showed intense immunopositive staining for CK 7/Vimentin/S-100; focal immune reactivity with P63 and weak immunoexpression of CD117 (c-kit), suggesting the final diagnosis of PAC. The results are in accordance with the interpretations made in previous studies.

PAC is an indolent tumor with low aggressiveness and good prognosis, rarely associated with regional and distant metastasis. Wide local excision or partial maxillectomy is the most common recommended aid of treatment for PAC affecting palate. Prosthetic rehabilitation using maxillary obturator can be done. The role of adjuvant postsurgical radiotherapy is not clearly defined.

CONCLUSION

Despite having striking morphological features, diagnosis of PAC is still a challenging task for the clinicians, because of close resemblance of some of its features to other salivary glands tumors and should be included in the differential diagnosis of a fixed, firm, painless palatal mass with intact overlying mucosa. To avoid diagnostic pitfalls and subsequent in appropriate management, clinicians must be aware of the overlapping microscopic features between PAC, AdCC and PA. Although the overall prognosis for PAC is favorable, the morbidity associated with the late diagnosis and the potential for local recurrence, regional or distant metastasis mandate clinical vigilance for timely diagnosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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