CASE REPORT

Histopathological spectrum of polymorphous low-grade adenocarcinoma

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ABSTRACT

Polymorphous low-grade adenocarcinomas (PLGA) are distinctive salivary gland neoplasms, with an almost exclusive propensity to arise from the minor salivary glands. PLGA frequently manifests as an asymptomatic, slow-growing mass within the oral cavity, which must be separated from adenoid cystic carcinoma and benign mixed tumor for therapeutic and prognostic considerations. We report a case of a 67-year-old male, who presented with a long-standing mass in the palate. This lesion was diagnosed as PLGA based on histopathological findings, which was further confirmed by the immunohistochemical marker.

Key words: Adenoid cystic carcinoma, minor salivary glands, polymorphous low-grade adenocarcinoma

INTRODUCTION

Polymorphous low-grade adenocarcinoma (PLGA) was recognized as a distinct entity in 1983 by Batsakis *et al*. Later in 1984 Evans and Batsakis coined the term PLGA.[1-3] PLGA is a malignant epithelial tumor characterized by cytological uniformity, morphological diversity, an infiltrative growth pattern and low metastatic potential.[4]

PLGA occurs almost exclusively in minor salivary glands, where it is found more frequently than adenoid cystic carcinoma (ACC). However, the incidence rate is lower than pleomorphic adenoma (PA) and mucoepidermoid carcinoma.[5] Clinically, PLGA presents as an indolent asymptomatic swelling but occasionally can be painful and even ulcerate. The most common location of PLGA is the palate, although other locations such as buccal mucosa have been described.[6]

PLGA is a rarely encountered salivary gland neoplasm, De Araujo *et al*. studied 26,960 cases of salivary gland tumors and the authors accepted only 431 (1.6%) as PLGAs.[6] While in India, Venkata and Irulandy studied 185 cases of minor salivary gland tumors and could classify only 18 cases (9.73%) as PLGA.[7]

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CASE REPORT

A 67-year-old male patient reported to our institute, with a chief complaint of swelling in the upper left back region of the palate from last 2 years. History revealed that the swelling was initially small in size and gradually achieved the present size, which was almost constant for past 1-year. Patient also gave a history of extraction of 26 due to caries and mobility.

No apparent swelling was noted on extraoral examination. Intraoral examination revealed a solitary, well-defined, dome-shaped swelling with bluish hue on the left postero-lateral part of the palate, measuring approximately 4 cm × 3 cm [Figure 1]. The swelling extended anterio-posterioly from the distal aspect of maxillary first premolar upto the maxillary tuberosity on the left side and medio-laterally from the midline of the palate upto the left alveolar margin. It was soft to firm in consistency, sessile, nontender, smooth surfaced and was not crossing the midline. It had caused slight obliteration of buccal vestibule and maxillary left permanent second molar showed Grade II mobility.

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Conventional radiographs did not reveal any bony changes [Figure 2], to further evaluate the soft tissue changes magnetic resonance imaging (MRI) were advised. The MRI report revealed a focally expansile mass in the posterior third of the hard palate and adjacent superior alveolus, involving the greater and lesser palatine foramina on the left side. The mass measured 2.9 (AP) × 2.7 (W) × 2.6 (H) cm in size. Superior-laterally, the lesion produced a focal bulge along the floor of the maxillary sinus, with a thin shell of intact cortical bone separating the mass from the sinus lumen [Figure 3]. The lesion did not cross the midline of the palate, nor did it involve the soft palate. Based on above findings, a provisional diagnosis of ACC was given.

Histopathological examination revealed a well-circumscribed, unencapsulated lesion with intact surface epithelium [Figure 4]. The tumor stroma consisted of both mucoid and hyaline areas. Tumor cells were arranged in various morphological patterns, such as solid, cribriform, duct-like and tubular patterns indicating morphodiversity and were separated by fibrovascular stroma [Figure 5]. The tumor cells were round to oval in shape with indistinct cell borders. The cytoplasm was scanty with round, oval or spindle shaped vesiculated nuclei [Figure 6]. At the tumor periphery, cells were arranged in a linear, single cell arrangement resembling "Indian file" or "beads on a string" pattern of infiltration [Figure 7]. No perineural invasion was noted in the present case.

To differentiate from ACC, immunohistochemistry (IHC) was performed which showed a strong positive reaction for vimentin [Figure 8]. Based on these findings, histopathological diagnosis of PLGA of the minor salivary gland was made.

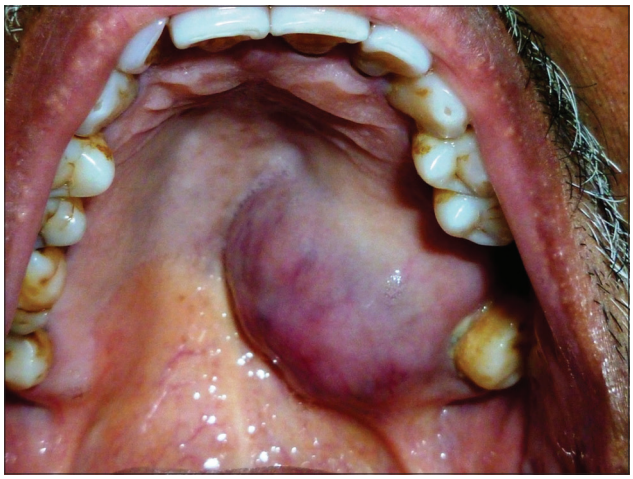

Figure 1: Intra-oral photograph showing a solitary, well-defined, dome-shaped swelling with bluish hue on the left postero-lateral part of the palate

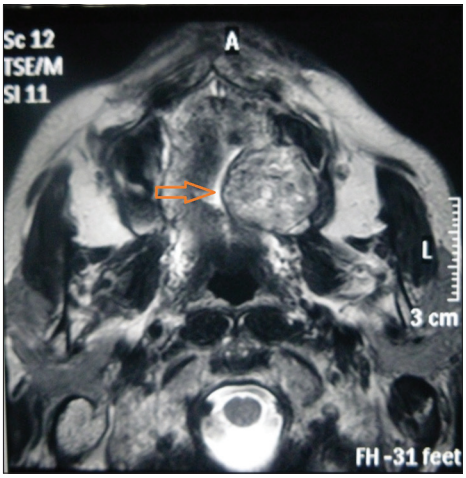

Figure 3: The magnetic resonance imaging report revealed focally expansile mass in the left half of the posterior third of the hard palate and adjacent superior alveolus, with a thin shell of intact cortical bone separating the mass from the maxillary sinus

DISCUSSION

PLGA has been recognized as a distinct salivary gland tumor that has a predilection to occur in the minor salivary glands and is associated with slow growth and indolent biology. PLGA occurs over a wide age range but does not seem to occur in the first or second decades of life. There is a female predilection, with a female to male ratio of 2:1.[8]

The review of the literature revealed that typical clinical presentation of PLGA is that of an asymptomatic mass located within the oral cavity. Clinical symptomatology ranges in

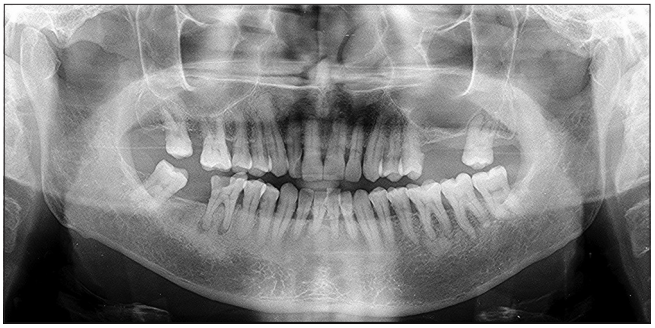

Figure 2: No significant bony changes noticed on orthopantomography

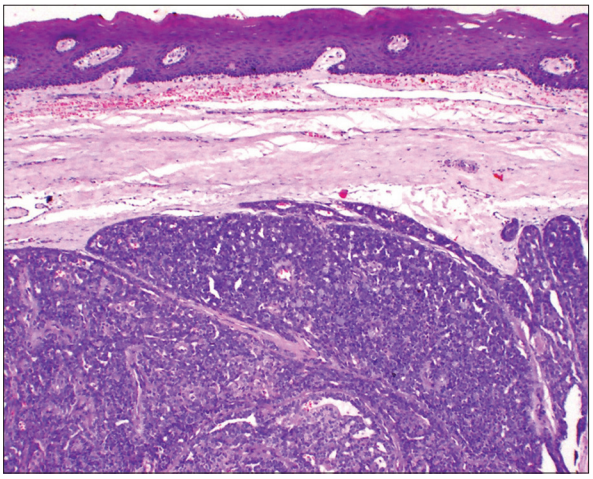

Figure 4: Lesional tissue comprising of glandular tissue separated by fibrous septa. Note-normal surface epithelium with lamina propria separating the lesional tissue (H&E stain, ×40)

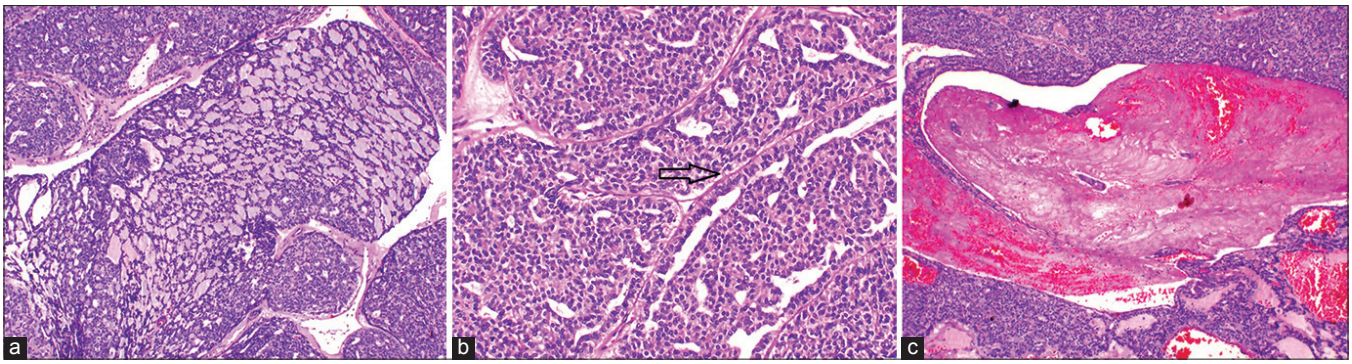

Figure 5: (a) Tumor cell arranged in a cribriform architectural pattern (H&E stain, ×100). (b) Tumor cell arranged in a ductal pattern (H&E stain, ×100). (c) Tumor tissue with mucoid pool and hemorrhagic areas (H&E stain, ×100)

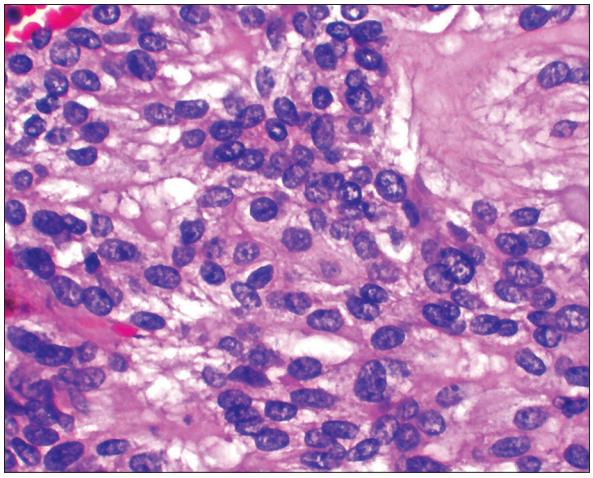

Figure 6: Uniform round to polygonal tumor cells with indistinct cell borders and vesiculated nucleus (H&E stain, ×400)

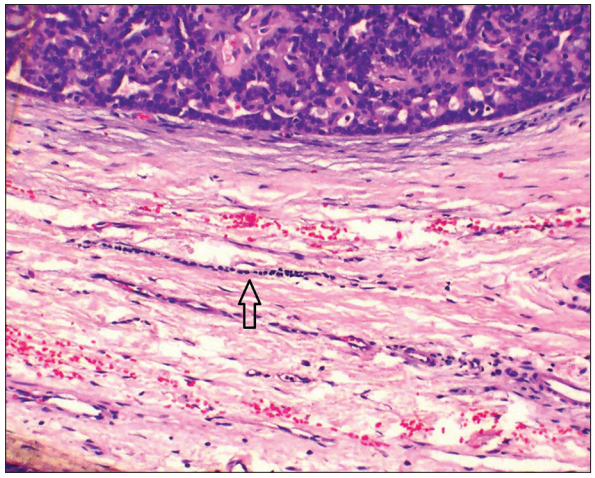

Figure 7: At the tumor periphery, the cells are arranged in a linear, single cell pattern resembling "Indian file" or beads on a string pattern of infiltration (H&E stain, ×100)

duration, from a few days to 40 years, with an average length of symptoms of 27 months. Patients who present with pain, bleeding or ulceration may not have more aggressive course nor are prone to develop recurrences. The tumor size ranges from 0.4 cm to 6.0 cm.[8]

Tumors of minor salivary glands may develop in the various parts of the head and neck region. However, high density of glandular tissue in the palate and in particular, the junction of hard and soft palate renders this location, the most frequent site for minor salivary gland neoplasms in the oral cavity.[9] In decreasing order of frequency, the PLGA occurs in the palate (32%); the soft palate (17%); the hard palate (16%); the lip (13%); the buccal mucosa (10%); the alveolar ridge (8%); and at mucosal sites not otherwise specified [NOS] (4%).[8] This tumor may also arise in major salivary glands (parotid), albeit very rarely.[9] In the present case, PLGA involved the posterio-lateral part of the hard palate.

Morphologic and IHC evidences indicate potential differentiation of both luminal and nonluminal cells (myoepithelial and basal cells) in PLGA. Ultrastructurally, some cases show only luminal cells, some both luminal and nonluminal cells while others are almost solely composed of myoepithelial cells.[10]

In the neoplastic state, myoepithelium has a lower proliferation than basal-type epithelial cells and secretes excess substances that inhibited tissue invasion and metastasis. These accumulated myxoid ground substances and basement membrane components as well as numerous proteinase inhibitors (maspin, α1-antitrypsin, TIMP-1 and protease nexin II) all contribute to an anti-invasive matrix for myoepithelial-rich salivary gland tumors. Hence, myoepithelial carcinomas (such as PLGA) exhibit lobulated and pushing rather than infiltrative tissue growth patterns and prolonged survivals despite distant metastases.[11]

Histopathological features

PLGAs are well-circumscribed but not encapsulated, however, infiltration into the adjacent salivary gland is quite common. Tumor cells are noted to be invading into and separating the lobular units of the residual minor salivary gland parenchyma as well as wrapping around the acini, but usually not invading individual acini or duct structures. Intact normal acini and ducts often can be identified to be completely surrounded by the tumor. This may occur in the center of the neoplasm, but

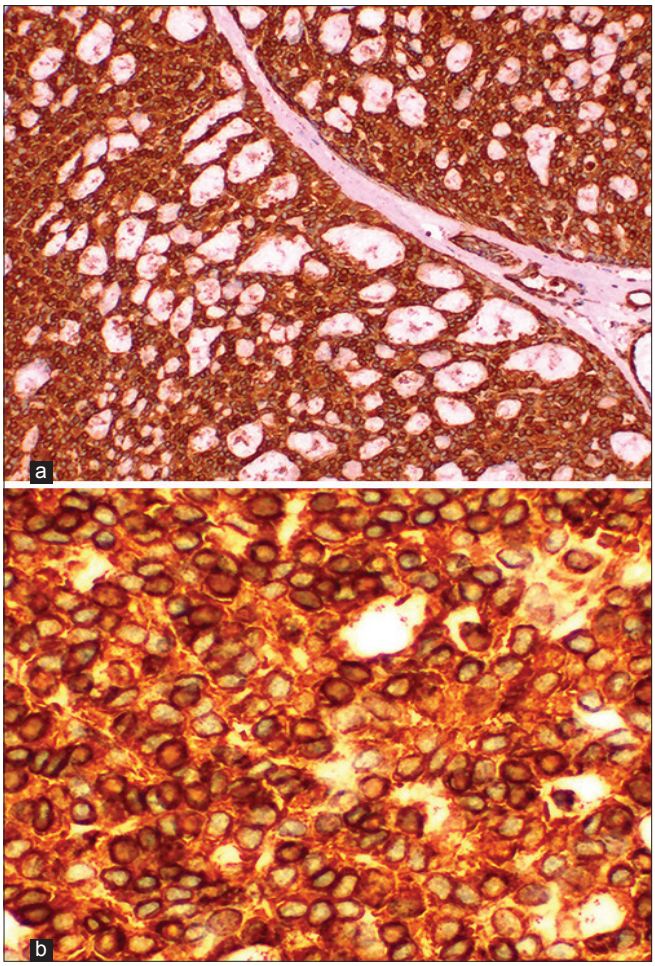

Figure 8: (a) Immunohistochemical staining with vimentin showing a strong positive reaction(IHC stain, x100). (b) Higher magnification of vimentin staining showing strong positive reaction in the lesional cells. (IHC stain, x400)

it is seen more commonly at the periphery of PLGA. The surface epithelium is usually intact and not involved by tumor, occasionally it may be ulcerated.[8]

PLGA may display a mixture of growth patterns within a single tumor, including solid islands; glandular profiles; tubules; trabeculae; cribriform nests and linear, single-cell, "Indian file" infiltration. Tubular areas are lined by one layer of cuboidal to columnar cells. Tumor cells often are arranged concentrically around a central nidus, creating a targetoid appearance. The nidus often is found to be a small nerve bundle (neurotropism) and is quite characteristic for PLGA. Perineural invasion is identified in nearly all cases, although it is accentuated more frequently in the cases with the targetoid growth pattern.[8] In our case, the perineural invasion was not noticed.

The tumor cells are uniformly round to polygonal, of small to medium size, with indistinct cellular borders and with abundant pale to eosinophilic cytoplasm. The nuclei are particularly distinctive, being uniformly round to ovoid and contain open, vesicular nuclear chromatin and inconspicuous to small nucleoli. The tumor cells are surrounded by a hyalinized, slightly eosinophilic stroma that occasionally displayed myxoid degeneration. A characteristic slate gray-blue stroma also is encountered frequently.[8]

Differential diagnosis

Diagnostic difficulties due to histopathologic overlap may occur with (PA) and ACC. These diagnostic difficulties often occur during frozen section examination or when the biopsy is small.[8]

Pleomorphic adenoma

Clinical features of PA affecting minor salivary glands overlap with those of PLGA and include absence of symptoms, slow growth, firm consistency, smooth texture, as well as, palatal predilection.[9]

The distinction between PLGA and PA usually can be made by identifying the presence of infiltrative growth, especially when combined with the presence of neurotropism. Furthermore, because mixed tumors of minor salivary glands most often are unencapsulated, differentiation from PLGA based on that feature is not reliable.[8]

Adenoid cystic carcinoma

It resembles PLGA in age, gender and palatal predilection; perineural invasion as well as the slow rate of growth, variability of growth patterns and infiltrative borders. In contrast, low-grade, dull pain is a frequent complaint with ACC and palatal tumors may appear ulcerated.[9]

Although perineural invasion may occur with either neoplasm, the targetoid pattern of invasion is unique to PLGA. While recognition of nuclear atypia is supportive of ACC, presence of cystic cavities, calcific deposits and papillary growth favors PLGA rather than ACC.[9] In contrast to PLGA, the cells in ACC tend to be smaller, with hyperchromatic nuclei, less cytoplasm, a higher nuclear to cytoplasmic ratio and coarser nuclear chromatin. The differences in nuclear morphology are particularly striking and are nearly pathognomonic.[8]

Both tumors may recur locally, however, ACC is more aggressive with a higher proliferative index, carries a greater potential for distant versus regional metastasis and has a worse prognosis. The surgical approach is also more radical and often combined with adjuvant radiotherapy for ACC highlighting the need to accurately differentiate between the two tumors.[9]

IMMUNOHISTOCHEMISTRY

Araújo *et al*. verified that vimentin could also be detected in PLGA in association with cytokeratins (CKs) 7, 8 and 14, which suggests that vimentin is not only found in neoplastic myoepithelial cells, but that it can be expressed by other cells originating from the intercalated ducts. This substantiates that the cells of PLGA originate from acini-intercalated duct cells.[12]

The same authors verified that only rare cells, in a small number of cases, presented positive reaction to muscle-specific actin, suggesting that myoepithelial cells rarely occur in this neoplasm and do not constitute the major cellular component of the tumor.[12] Hence, it can be concluded that PLGA originates from acini-intercalated duct cells and thus shows positivity for vimentin.

Many IHC studies have attempted to develop a useful marker for PLGA or to differentiate it from other histologically similar tumors.

Darling *et al*. in their review concluded that the only marker which presents a clear difference is vimentin, which is negative in ACC and positive in PLGA. No other markers investigated have shown a clear difference between the two tumors as the results have been variable.[5]

According to de Araujo *et al*., uniformly positive vimentin and CK 7 staining is sufficient for a final PLGA diagnosis. S100 is also positive in almost all of the cells, but this characteristic is only diagnostically supportive.[6]

In conclusion, vimentin may be the sole marker allowing distinction between PLGA and ACC.[2] In the present case, vimentin was used as an IHC marker to differentiate PLGA from ACC, which showed a strong positive reaction, which further confirmed the diagnosis of PLGA [Figure 8].

TREATMENT AND PROGNOSIS

Malignant salivary gland neoplasms including PLGA affecting the palate are generally treated with wide local excision or partial maxillectomy as needed to achieve complete tumor clearance. After surgery prosthetic rehabilitation with an obturator is preferable in the setting of a malignancy where surgical margins should be closely monitored for recurrence.[9] In the present case, the patient was treated by partial maxillectomy and rehablilated with a maxillary obturator. To monitor the recurrence, the patient was kept on regular follow-ups for past 6 months, however, no recurrence has been noted.

Although known to have a good prognosis, when adequately followed, the incidence of local recurrence with PLGA may be as high as 33%.[13] Patients in case series published by Castle *et al*. developed recurrences from 2 to 14 years after the initial presentation, with an average 7.2 years to the discovery of a recurrence. Hence, periodically patient assessment for the recurrent tumor is prudent for the rest of the patient's life.[8]

CONCLUSION

PLGA, which occurs predominantly in minor salivary glands shares many clinical features with other minor salivary gland neoplasms 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 inappropriate management, the pathologist should be aware of the overlapping microscopic features between PLGA, ACC and PA. The only IHC marker which presents a clear difference is vimentin, which is negative in ACC and positive in PLGA.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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