INVITED REVIEW

Polymorphous low grade adenocarcinoma

Chatura KR
Department of Pathology, Jagadguru Jayadeva Murugarajendra Medical College, Davangere, Karnataka, India

Address for correspondence:
Dr. Chatura KR,
Department of Pathology,
Jagadguru Jayadeva Murugarajendra Medical College, Davangere - 577 004, Karnataka, India.
E-mail: chaturakr@gmail.com

Received: 12-10-2014
Accepted: 15-04-2015

ABSTRACT

Polymorphous low-grade adenocarcinoma (PLGA), is a rare, salivary gland intraoral tumor with complexities in diagnosis and this review highlights the difficulties.

Key words: Lobular carcinoma, Polymorphous low-grade adenocarcinoma, terminal duct carcinoma

INTRODUCTION

Salivary gland tumors are a relatively rare and morphologically diverse group of lesions. Although most clinicians and pathologists will have encountered the more common benign neoplasms, few have the experience of all types of salivary cancers, which are best managed in specialist centers.[1] Polymorphous low-grade adenocarcinoma (PLGA) is one such tumor, misunderstood, underdiagnosed, controversial in nomenclature and unpredictable in behavior. This review highlights areas of diagnostic difficulty, controversy in nomenclature and immunohistochemistry (IHC).

PLGA was simultaneously described as terminal duct carcinoma by Batsakis *et al*.,[2] and as lobular carcinoma by Freedman and Lumerman[3] in1983, names that alluded to its putative origin in intercalated (terminal) ducts and to its microscopic similarity to lobular carcinoma of the breast. Subsequently, Evans and Batsakis in 1984 coined the term PLGA which describes its variable morphological appearances and apparent low-grade behavior.[4]

Most PLGAs involve minor salivary glands of the palate, buccal mucosa and upper lip. The retromolar region, floor of mouth, posterior tongue and nasal cavity can also be affected. PLGA is rare in major glands, but has been reported as a primary lesion or, more commonly, as the carcinomatous component of carcinoma ex pleomorphic adenoma (PA).[5,6] PLGAs arising in major salivary glands have characteristics similar to those originating in minor salivary glands.[7]

Access this article online

Quick Response Code:

Website: www.jomfp.in

DOI: 10.4103/0973-029X.157206

PLGA occurred over a wide age range, but did not seem to occur in the 1st or 2nd decades of life in a single comprehensive study of 164 cases representing the largest single series of its kind to date (Medline 1966–1998). Female: Male ratio was 2:1 and ages ranged from 23 to 94 years. In decreasing order of frequency, 32% occurred in the palate, 17% in soft palate, 16% in hard palate, 13% in lip, 10% in buccal mucosa, 8% in alveolar ridge and 4% at mucosal sites, not otherwise specified (NOS).[8] PLGA has also been described in children.[5]

In the Armed Forces Institute of Pathology (AFIP) series, PLGA represents about 7% of minor salivary gland tumors and 20% of those that are malignant. They suggest that it is twice as common as adenoid cystic carcinoma (ACC) in the minor glands and may be the third most common of all salivary tumors after PA and mucoepidermoid carcinoma.[9]

The percentage of PLGAs among malignant minor salivary gland tumors (MMSGTs) varied among the studies, ranging from 0 to 46.8%. PLGA rates have varied over the period studied and have most recently increased. The frequency of reported PLGA cases also varied from 0.0 to 24.8% by the country in which the MMSGT studies were performed. The PLGA percentages also varied significantly by continent, with frequencies ranging from 3.9 in Asia to 20.0% in Oceania.[10]

MORPHOLOGY

PLGA is characterized by invasive growth, morphological diversity (hence the term polymorphous) and cytological uniformity. The morphological patterns typically include lobular solid nests admixed with cribriform, trabecular and focal papillary cystic areas. The ductal elements are usually small, apparently single layered and resemble intercalated (terminal) ducts. In areas, usually at the periphery of the tumor, there are cells aligned in single files that resemble 'beads on a string'.[11]

The tumor has a characteristic pattern with columns and rows of single cells infiltrating adjacent tissues and salivary gland

and extending upto the overlying epithelium [Figure 1]. At low power, the appearance is of swirling lobules and columns of tumor enveloping adjacent structures.[1]

The tumor stroma is composed of fibrous tissue that shows varying degrees of hyalinization and myxoid change; however, the chondromyxoid matrix that typifies PA is absent. Stromal mucinosis and elastosis may be observed along with intratumoral hemorrhage. PLGA is invasive and locally destructive. There is usually destruction of native seromucinous glands and lobules of the gland are incarcerated within the body of the neoplasm [Figure 2]. The concentric whorling is seen around small neurovascular bundles producing a targetoid appearance [Figure 3].This perineural invasion (PNI) or neurotropism is a characteristic feature of PLGA. Similar whorling is occasionally found around collecting ducts.[11] PNI can be identified in about 30% of cases.[5]

Bone invasion may be seen in large lesions in the hard palate[5] [Figure 4]. Palatal lesions eventually impinge upon the maxillary bone and cause bone resorption and latterly medullary invasion.[11]

One of the most characteristic features of PLGA is the nuclear uniformity. The cells are cytologically bland and can be cuboidal, columnar, or spindled with a mixture being quite common. They have scant to moderate amounts of amphophilic or eosinophilic cytoplasm. Occasional tumors have mucus cells, clear cells or oncocytic cells; but these are typically a minor component in such cases. Even in these different cell types, the nuclei are uniform, round to ovoid, with finely dispersed or ground-glasstype nuclear chromatin [Figure 5]. The nuclei are typically ovoid in profile and have pale, 'washed out' chromatin, with an appearance resembling that of papillary thyroid carcinoma[12] and the impression that the section has been inadequately stained.[13]

Mitotic activity is inconspicuous.[12] Mitotic figures are rare, with an average mitotic count of 1/10 HPF. Atypical mitotic figures are not a feature of PLGA.[5] Necrosis is not seen.[6]

DIFFERENTIAL DIAGNOSIS

Its propensity for occurrence in the palate and indolent clinical features make confusion with PA or ACC even more likely. Seen in entirety, the diversity may establish the diagnosis, but in small incisional biopsies, where only a single pattern may be apparent, the lesion can easily be mistaken for a PA, ACC or a basal cell lesion.[1]

All these tumors share similar morphologic features and to a large extent immunohistochemical findings. These tumors consist of cells with limited nuclear pleomorphism, absent to low mitotic activity and absence of necrosis. As such, in the presence of limited tissue sampling that typifies the initial testing modalities, including fine-needle aspiration biopsy

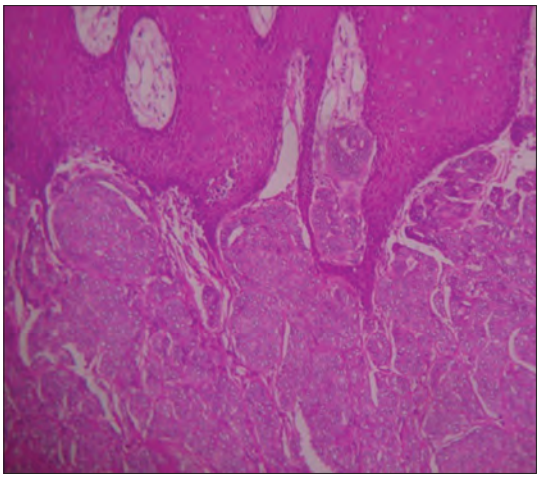

Figure 1: Histopathological image shows tumor extending upto the overlying epithelium (H&E stain, ×100). H&E = Hematoxylin and eosin

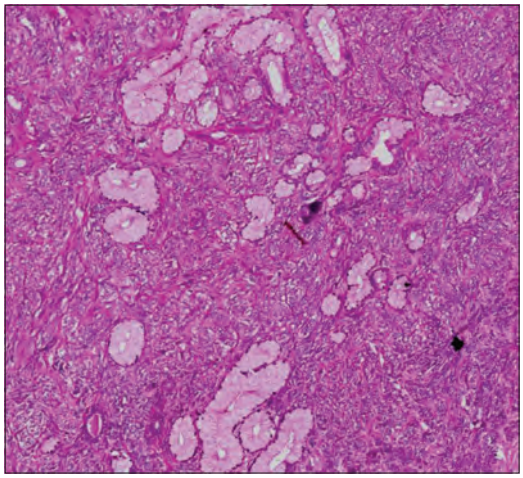

Figure 2: Histopathological image shows lobules of salivary gland incarcerated within the body of the neoplasm (H&E stain, ×100)

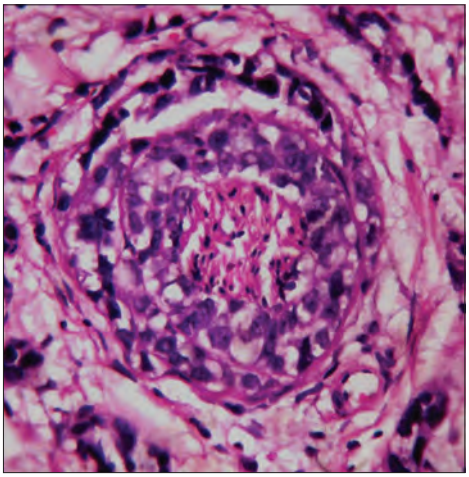

Figure 3: Histopathological image shows whorling around small neurovascular bundles; a targetoid appearance (H&E stain,×400)

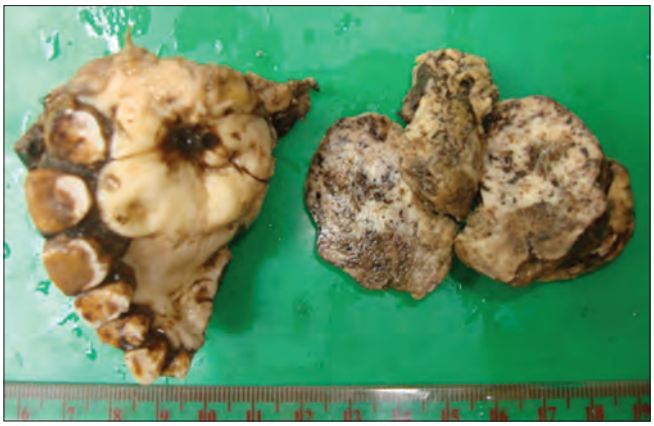

Figure 4: Gross image shows bone invasion in a large tumor in the hard palate

and/or incisional biopsy, it often is not possible to differentiate a benign from MMSGT which is often predicated on the presence or absence of invasion. The diagnostic difficulties arise in needle or incisional biopsies, where the periphery of the tumor is not available to determine whether infiltrative growth is present or absent.[14]

Unfortunately, when surgeons perform biopsies, they usually obtain the tumor from the center of the lesion, not the periphery, so it is often difficult to assess for invasion.[12]

Other than metastasis, definitive features of malignancy in minor salivary gland neoplasms are predicted on infiltrative growth. By definition, invasive growth occurs at a lesion's periphery and includes invasion into nonneoplastic seromucous glands, soft tissues and/or bone, PNI and lymphovascular invasion. Specific aspects of a tumor's growth, such as envelopment of residual seromucous glands by PLGA, may factor into the differential diagnosis of a given lesion.[14]

Unfortunately, the characteristic nuclear features are often not identifiable in small biopsy specimens, as these types of specimens tend to be crushed and distorted. Also, the low-grade nuclei can make it difficult to interpret in tumors with glandular growth patterns, particularly in frozen sections. Recognizing infiltrative growth and PNI thus becomes the most important diagnostic feature in many cases.[12]

Certain cytologic features may suggest a specific diagnosis, such as ACC characteristically contains abundant myoepithelial (abluminal) cells with increased nuclear-to-cytoplasmic ratio and basaloid (hyperchromatic) angulated nuclei without identifiable nucleoli. Similar nuclear features, however, can be present in basal cell adenoma and even in PA. In contrast, basaloid hyperchromatic nuclei are not generally evident in PLGA, which typically consists of cells with vesicular chromatin and inconspicuous small nucleoli.[14]

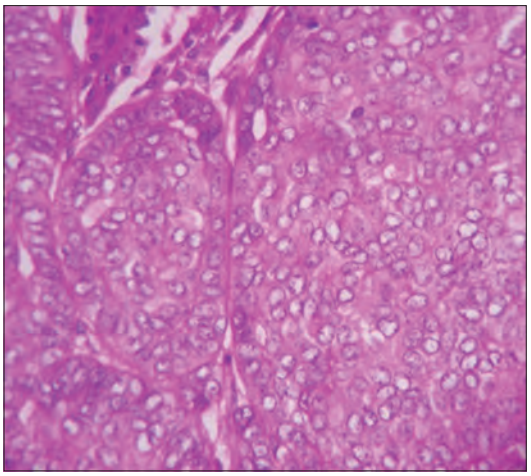

Figure 5: Histopathological image shows uniform nuclei, round to ovoid, with ground-glass type nuclear chromatin (H&E stain,×400)

Like PLGA, ACCs can be architecturally heterogeneous with tubular, cribriform growth patterns occurring in varying quantities. Cribriform growth can be seen in PLGA, but if a cribriform pattern is seen throughout the lesion, this suggests ACC. Cyst formation and calcific deposits are also more, in keeping the diagnosis with PLGA than with ACC.[12]

Separating PLGA from ACC can also be very challenging in biopsy samples. PNI is a prominent feature for both of these salivary gland malignancies; however, a targetoid arrangement of PNI is more typical of PLGA.[12] ACC have more extensive PNI and stromal invasion.[5]

In many areas and at the cytologic level, it is often difficult if not impossible to distinguish PLGA from PA. The most useful distinguishing features are the lack of tubules with two cell layers or squamous differentiation, lobules of cartilage and calponin and glial fibrillary acidic protein (GFAP) immunostaining in PLGA. PNI or stromal invasion is not seen in PA. This distinction may be difficult or impossible in small biopsies that does not reflect the heterogeneous patterns or infiltrative nature or PNI of PLGA or contains focal stromal change simulating a myxochondroid matrix[6] or in cytologic aspirates and the possibility of a PLGA should be excluded when examining minor salivary gland tumors with the features of a PA.[5]

A fact worth filing is that PAs of minor salivary gland are not often encapsulated and may have focal extensions into adjacent minor salivary gland that are seemingly infiltrative when interpreted in a narrow field context. A low power appreciation of the circumscribed nature of PAs compared with the widely infiltrative nature of PLGA and common PNI are useful histologic discriminants as is the intense staining of PA for muscle markers of myoepithelial differentiation.[6]

GRADING

Is grading of salivary gland tumors always necessary? The answer is no. Many tumor types are for the most part definitionally high risk both histologically and biologically (i.e., conventional salivary duct carcinoma, squamous cell carcinoma and small cell neuroendocrine carcinoma) or low risk (i.e., epithelial-myoepithelial carcinoma and PLGA). The caveat is that high-grade (HG) versions of 'intrinsically' low-grade tumors do exist as do low-grade versions of typically HG tumors. Both pathologists and clinicians need to be aware of these variants.[15] Thus:

- The usual example of such a tumor type may not need to be qualified with a grading descriptor
- An unusually HG or low-grade variant of a tumor should be conveyed in the pathological report.

Evans and Luna showed that 15% of cases had cervical metastases, 7.5% had distant metastases and 12.5% of patients died of disease.[16]As the name suggests, PLGA is regarded as a low-grade neoplasm, but in the experience of others, behavior is unpredictable and similar or worse than mucoepidermoid carcinoma. An infiltrative pattern is typical and occasional cases infiltrate widely with widespread destruction at first diagnosis. Thus, it is unclear why this lesion deserves the accolade 'low-grade' in its name and the more descriptive term polymorphous adenocarcinoma is preferred, which is not suggestive of behavior and may help to avoid inappropriately conservative management. There is no good reason why this tumor, whose behavior is unpredictable, should be the only salivary gland tumor with a statement of grade in its name. The lesion should be managed in the same way as other salivary gland lesions, based on stage and a careful consideration of the histological features.[17]

HG transformation (dedifferentiation) refers to the transformation of a histologically low-grade neoplasm to one that is HG by morphology and other characteristics and in which the original line of differentiation is no longer evident. The phenomenon of HG transformation has been recognized in a variety of salivary gland malignancies including acinic cell carcinoma, ACC, PLGA and mucoepidermoid carcinoma. Although HG transformation is always associated with tumor progression, there are heterogeneous variable molecular genetic events that regulate it.[18]

PLGA is considered to be of low-grade malignant potential in that nodal metastases are seen in only a minority and distant spread is rare. Even more unusual is the transformation of PLGA to a histologically HG carcinoma, that is, dedifferentiation. PLGA was first described relatively recently and as experience with it continues to accumulate, it is becoming clear that late recurrences and metastases, whilst still infrequent, may not be quite as rare as previously thought. Reports of histological transformation are even scarcer and most occurred at least 13 years after PLGA was initially recognized. It is a real possibility that this phenomenon, like clinical progression, may also be encountered more often as time passes (personal observation in two cases in 10 years). Therefore, we believe that, whilst PLGA is certainly far less aggressive than, for example, ACC, it nevertheless remains a true malignancy with a potential to prove fatal in a minority of patients.[19]

IHC

The complexity of salivary tumors is largely due to the participation of neoplastic myoepithelial cells which exhibit remarkable phenotypic and secretory abilities. The proportions and morphologic appearances of ductal and myoepithelial cells, type of tumor matrix and relation of tumor cells with extracellular matrix is what defines entities such as PAs, myoepitheliomas, ACC, epithelial/myoepithelial carcinoma and basal cell adenocarcinoma. Other lesions such as PLGA, acinic cell carcinoma and hyalinizing clear cell carcinoma show little or no myoepithelial differentiation. Understanding this so-called morphogenetic concept is quite important in the diagnosis of these tumors.[5]

The presence of myoepithelial cells in PLGA is controversial. Some authors consider myoepithelial cells to be an integral cell component in addition to ductal cells in PLGA; other authors feel that myoepithelial cells are limited or even absent in PLGA. For any given case of PLGA, IHC staining for myoepithelial differentiation may not be substantially different from the PA, basal cell adenoma and ACC to allow for differentiation.[14]

Since the 1990s, many studies have attempted to develop a useful marker for PLGA or to differentiate it from other histologically similar tumors. To date there has been no reliable molecular marker to distinguish PLGA from other MMSGTs [Table 1].[20] Controversy on this subject persists in the literature. Some authors believe that IHC does not have any proven diagnostic value for identifying PLGA. Some

Table 1: Comparison of immunohistochemical markers in PLGA and ACC

Immunohistochemical marker	PLGA	ACC
Carcinoembryonic antigen (CEA)	+/−	+
Epithelial membrane antigen (EMA)	+	+
S100 protein	+	+/−
Vimentin	+	−
Alpha-smooth muscle actin (ASMA)	unknown	+
Muscle specific actin (MSA)	+/−	+
P53	+/−	+/−
Proliferative nuclear cell antigen (PCNA)	+/−	+/−
MIB-1 (Ki-67)	+/−	+
C-erbB-2	−	+/−
Glial fibrillary acidic protein (GFAP)	−	unknown

have successfully used IHC in difficult cases or to confirm a histological diagnosis.[10,20]

A consistent and significant difference in GFAP reactivity between PLGA and PA was seen when standardized techniques are used. Thirty-six cases of PA were strongly positive for GFAP, 31 cases of PLGAs were negative and 11 showed faint patchy reactivity in luminal cells. Therefore, the use of GFAP should be considered when the presence of overlapping architecture, background and cellular features in a neoplasm of minor salivary glands presents the pathologist with a diagnostic dilemma for differentiation of PLGA versus PA.[21]

Distinguishing ACC from PLGA of the salivary glands is important for their management. The expression of several myoepithelial and basal/stem cell markers by IHC, in 23 ACC and 24 PLGA, were studied to identify the most useful marker or combination of markers that may help their diagnoses. The results were analyzed using hierarchical cluster analysis and χ^2 test for trend. Hierarchical clustering of smooth muscle actin, calponin, smooth muscle myosin heavy chain and metallothionein was virtually identical ($\kappa \leq 0.0035$), suggesting no significant advantage to their use in combination than individually. Diffuse smooth muscle actin expression showed the highest accuracy (91.5%) and positive predictive value (95.2%) for ACC. Thus, diffuse expression of these markers was highly predictive of ACC, whereas maspin and p63 were frequently expressed in both tumors. In differentiating ACC from PLGA, smooth muscle actin as a single ancillary test in support of the histological findings, appears to be as efficient as multiple immunohistochemical tests.[22]

PLGA appears to show little evidence of myoepithelial differentiation, although this view has been challenged. ACCs consistently stained positive for putative myoepithelial markers. PLGAs lacked this staining pattern, leading to the suggestion that there was no evidence of myoepithelial differentiation in PLGA. p63 staining results were compatible with the suggestions that the neoplastic cells in PLGA represent either a population of p63-positive epithelial stem/reserve cells similar to the basal cells of stratified epithelium, or modified myoepithelial cells. However, the involvement of myoepithelial cells in the histogenesis of PLGA cannot be ruled out. p63 is strongly expressed in basal cell adenoma of parotid origin; and in ACC and PLGA. Canalicular adenoma did not demonstrate p63 staining, consistent with this tumor's putative luminal ductal cell differentiation. Given the staining pattern of the tumors examined, p63 does not appear to be an ideal marker for distinguishing between ACC, PLGA and basal cell adenoma.[23]

It is important to note that tumor cytology and histology are usually sufficient for a final diagnosis. However, IHC is valuable in unclear PLGA cases. Uniformly positive vimentin and CK7 staining, except for the rare two-layer ducts, is sufficient for a final PLGA diagnosis. S100 is also positive in almost all of the cells, but this characteristic is only diagnostically supportive.[10]

PLGA are indolent neoplasms that are unlikely to cause death. Unlike ACC, PLGA are treated by conservative wide excision. Therefore, it is especially critical to diagnose a PLGA rather than ACC in any location, but most notably in the palate as the latter diagnosis would result in a more radical excision of the hard palate.[6]

Despite our improved understanding of this entity over time, worldwide differences found amongst the studies indicate that diagnosing PLGA remains challenging, probably because histological and cytological criteria are not uniformly applied.[10]

CONCLUSION

PLGA is a challenge for pathologists, especially beginners and on limited material. Attention to morphological details, IHC and experience provide confidence in approaching these rare and unexpected neoplasms.

REFERENCES

1. Speight PM, Barrett AW. Salivary gland tumours. Oral Dis 2002;8:229-40.
2. Batsakis JG, Pinkston GR, Luna MA, Byers RM, Scuibba JJ, Tillery GW. Adenocarcinoma of the oral cavity: A clinicopathologic study of terminal duct carcinomas. J Laryngol Otol 1983;97:825-35.
3. Freedman PD, Lumerman H. Lobular carcinoma of intraoral minor salivary glands origin. Report of twelve cases.Oral Surg Oral Med Oral Pathol 1983;56:157-66.
4. Evans HL, Batsakis JG. Polymorphous low-grade adenocarcinoma of minor salivary glands. A study of 14 cases of a distinctive neoplasm. Cancer 1984;53:935-42.
5. Perez-Ordonez B. Selected topics in salivary gland pathology. Curr Diagn Pathol 2003;9:355-65.
6. Zarbo RJ. Salivary gland neoplasia: A review for the practicing pathologist. Mod Pathol 2002;15:298-323.
7. Nagao T, Gaffey TA, Kay PA, Minato H, Serizawa H, Lewis JE. Polymorphous low-grade adenocarcinoma of the major salivary glands: Report of three cases in an unusual location. Histopathology 2004;44:164-71.
8. Castle JT, Thompson LD, Frommelt RA, Wenig BM, Kessler HP. Polymorphous low grade adenocarcinoma: A clinicopathologic study of 164 cases.Cancer 1999;86:207-19.
9. Ellis GL, Auclair RL. Tumors of the salivary glands. Atlas of Tumor Pathology; 3rd ed. Washington: Armed Forces Institute of Pathology; 1996.
10. de Araujo VC, Passador-Santos F, Turssi C, Soares AB, de Araujo NS. Polymorphous low-grade adenocarcinoma: An analysis of epidemiological studies and hints for pathologists. Diagn Pathol 2013;8:6.
11. Paleri V, Robinson M, Bradley P. Polymorphous low-grade adenocarcinoma of the head and neck. Curr Opin Otolaryngol Head Neck Surg 2008;16:163-9.
12. McHugh JB, Visscher DW, Barnes LE. Update on selected salivary

gland neoplasms. Arch Pathol Lab Med 2009;133:1763-74.
13. Wenig BM, Gnepp DR. Polymorphous low-grade adenocarcinoma of minor salivary glands. In: Ellis GL, Auclair PL, Gnepp DR, editors. Surgical pathology of the salivary glands. Philadelphia: W. B. Saunders; 1991.p. 390-411.
14. Turk AT, Wenig BM. Pitfalls in the biopsy diagnosis of intraoral minor salivary gland neoplasms: Diagnostic considerations and recommended approach. Adv Anat Pathol 2014;21:1-11.
15. Seethala RR. An update on grading of salivary gland carcinomas. Head Neck Pathol 2009;3:69-77.
16. Evans HL, Luna MA. Polymorphous low-grade adenocarcinoma: A study of 40 cases with long-term follow up and an evaluation of the importance of papillary areas. Am J Surg Pathol 2000;24:1319-28.
17. Speight PM. Update on diagnostic difficulties in lesions of the minor salivary glands. Head Neck Pathol 2007;1:55-60.
18. Skalova A, Vanecek T, Simpson RH, Michal M. Molecular advances in salivary gland pathology and their practical application. Diagn Histopathol 2012;18:388-96.
19. Simpson RH, Pereira EM, Ribeiro AC, Abdulkadir A, Reis-Filho JS. Polymorphous low-grade adenocarcinoma of the salivary glands with transformation to high-grade carcinoma. Histopathology 2002;41:250-9.
20. Darling MR, Schneider JW, Phillips VM. Polymorphous low-grade adenocarcinoma and adenoid cystic carcinoma: A review and comparison of immunohistochemical markers. Oral Oncol 2000;38:641-5.
21. Curran AE, White DK, Damm DD, Murrah VA. Polymorphous low-grade adenocarcinoma versus pleomorphic adenoma of minor salivary glands: Resolution of a diagnostic dilemma by immunohistochemical analysis with glial fibrillary acidic protein. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;91:194-9.
22. Prasad ML, Barbacioru CC, Rawal YB, Husein O, Wen P. Hierarchical cluster analysis of myoepithelial/basal cell markers in adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma. Mod Pathol 2008;21:105-14.
23. Edwards PC, Bhuiya T, Kelsch RD. Assessment of p63 expression in the salivary gland neoplasms adenoid cystic carcinoma, polymorphous low-grade adenocarcinoma, and basal cell and canalicular adenomas.Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004;97:613-9.

How to cite this article: Chatura KR. Polymorphous low grade adenocarcinoma. J Oral Maxillofac Pathol 2015;19:77-82.

Source of Support: Nil. **Conflict of Interest:** None declared.