Review Article

Polymorphous Low-Grade Adenocarcinoma of the Salivary Glands – A Review

*[1]Divya Khosla, [1]Renu Madan, [1]Shikha Goyal, [1]Narendra Kumar, [1]Rakesh Kapoor.

[1]Department of Radiotherapy, Postgraduate Institute of Medical Education and Research, Regional Cancer Centre, Chandigarh, India

Abstract

Polymorphous low-grade adenocarcinoma (PLGA) is a rare neoplasm with an indolent course that occurs mainly in minor salivary glands and rarely in major salivary glands. It is characterised by morphological diversity hence the term polymorphous has been used. Diagnosis is often challenging due to variable microscopic growth patterns. The most common clinical presentation is asymptomatic painless mass which is slow-growing. The treatment of choice is wide surgical excision with negative margins. The role of radiotherapy is still not clear but considered in cases with positive margins and advanced stage. In this article, we review the clinical presentation, pathological features, treatment and prognosis of this rare entity.

Keywords: Polymorphous Low-grade Adenocarcinoma; Prognosis; Salivary Gland Neoplasms; Surgery.

Introduction

Polymorphous low-grade adenocarcinoma (PLGA) is an uncommon malignant low-grade epithelial tumour exclusively of minor salivary glands characterized by a triad of cytological uniformity, morphological diversity and an infiltrative growth pattern[1]. It was first described by Freedman and Lumerman in 1983 as lobular carcinoma of salivary gland origin because of their microscopic similarity to the breast tumours of the same name[2] . Batsakis *et al.* [3] in 1983 designated this neoplasm as terminal duct carcinoma in a clinic-pathological study of 12 patients. In 1984, Evans and Batsakis[4] labelled this entity as polymorphous low-grade adenocarcinoma in their study of 14 cases. The location of the neoplasm was intraoral in all cases (palate in 11, the buccal mucosa in 2, and the posterior mandibular area in 1).

PLGAs occur almost exclusively in minor salivary glands and rarely in major salivary glands. The most common site of occurrence is the palate which accounts for about 60% of all cases. The other common sites of occurrence include buccal mucosa, lip, alveolar mucosa, retromolar trigone and floor of the mouth. It can occur rarely in major salivary and lacrimal glands, nasal cavity, nasopharynx, paranasal sinuses and tonsillar region[5-7].

Epidemiology

Salivary gland neoplasms comprise 6% of all head and neck tumours[8]. In a series of 6982 cases of salivary gland neoplasms in oral and maxillofacial regions, PLGA accounted for about 1% of all malignant tumours[9]. It occurs over a wide range of age groups

Corresponding Author: *Divya Khosla
[1]Department of Radiotherapy, Postgraduate Institute of Medical Education and Research, Regional Cancer Centre, Chandigarh, India. Email: dr_divya_khosla@yahoo.com

Access this article online

Quick Response Code:

Website: www.nigerianmedjournal.org

How to cite this article: Khosla D, Madan R, Goyal S, Kumar N, Kapoor M. Polymorphous Low-Grade Adenocarcinoma of the Salivary Glands - A Review. Niger Med J 2021; 62; (2):49-53.

from 16-94 years with a mean age of presentation at 59 years[6,7]. It has been rarely reported in the first and second decade[10-13]. It shows female preponderance with a female to male ratio of 2:1[6,7].

Clinical Presentation

The most common presentation is asymptomatic painless mass which is slow-growing and duration may vary from weeks to years. Rarely bleeding, ulceration or telangiectasia may occur. Lymphatic and haematogenous metastases are rare. Regional metastasis rate varies from 5% to 25% in various series[5,7,14,15]. Distant metastasis rate varies between 0.6 to 7.5%[6,7,15]. The largest series comprising of 460 cases of head and neck PLGA has been published by Patel et al., mean age at diagnosis was 61.3 years with female predilection (female-to-male ratio of 2.15:1), and regional metastasis was seen in 25% and distant metastasis in 4.3% of patients[15].

PLGA can arise rarely in major salivary glands. It may occur de novo or as a component of carcinoma ex pleomorphic adenoma. Nagao et al. [16]reported three cases of PLGAs arising in major salivary glands and stated that PLGAs arising in major salivary glands have clinicopathological and immunohistochemical characteristics similar to PLGAs arising in minor salivary glands. PLGA can rarely de-differentiate into a high-grade neoplasm. To the best of our knowledge, six cases of transformation of PLGA to higher histological grade have been reported in the literature[17-20]. Pelkey and Mills[17] reported two cases of transformation of PLGA to higher grade neoplasm after 17 and 26 years, respectively. A high-grade transformation occurred over a protracted clinical course associated with multiple recurrences that were treated with surgery and radiotherapy.

Pathology

PLGAs appear as well-circumscribed non-encapsulated lobulated mass with infiltration into the adjacent salivary gland. It is characterized by a triad of infiltrative growth patterns, cytological uniformity and architectural diversity[1]. The various architectural growth patterns include solid, trabecular, lobular, glandular, micro-cystic, cribriform, fascicular, tubular and papillary. One of the distinctive features of PLGA is the presence of morphological diversification between tumours and within the tumour[21]. The diverse growth patterns and a stromal component may complicate the diagnosis. The other characteristic feature is nuclear uniformity. The tumour cells are cytologically bland, small to medium size, round to polygonal, with scant to moderate amounts of pale to eosinophilic cytoplasm[1]. There may be foci of mucus, clear, squamous or oncocytic cells. The nuclei are round to oval with vesicular nuclear chromatin and inconspicuous nucleoli[22]. The central portion of the tumour consists of solid or lobulated growth patterns with tubular and glandular elements often observed at the periphery. Stroma may display areas of mucinosis or hyalinization. PLGA may exhibit an Indian file pattern of perineural invasion with cords of cells concentrically arranged around nerves producing a characteristic targetoid appearance[22].

Immunohistochemically, the neoplastic cells of PLGA exhibit moderate to strong immunoreactivity to cytokeratin (CK), vimentin, S-100 protein, carcinoembryonic antigen (CEA) and Bcl-2[6,23,24]. The expression of CKs 8,18 and 7, indicates that PLGA originates from cells located at the acinar-intercalated duct junction[25]. Significant galectin 3 expression has been reported in PLGA[26,27]. Various studies have proven that PLGA is nonreactive to glial fibrillary acid protein (GFAP) [6,28-31]. Thus, GFAP can be considered when there is a diagnostic dilemma of differentiating PLGA from pleomorphic adenoma (PA)[31].

The presence of polymorphism makes the diagnosis of PLGA challenging in small biopsy specimens and the differential diagnosis includes pleomorphic adenoma and adenoid cystic carcinoma (ACC). Pleomorphic adenomas are usually well-circumscribed but non-encapsulated and lack infiltrative growth patterns as seen in PLGA. Presence of perineural invasion and absence of cartilage favour PLGA. Chondromyxoid stroma is observed in pleomorphic adenoma, though myxoid tissue may be present in both tumours. GFAP may assist in the differential diagnosis of PLGA versus pleomorphic adenoma[31].

The prognosis and biological behaviour of ACC are worse than PLGA, thus making differentiation important for diagnostic purposes and therapeutic decision making. ACC of salivary glands is characterized by slow growth, local infiltration, perineural invasion and tendency to late recurrence and distant metastasis. PLGA can be differentiated from ACC based on cytological features. Papillary growth patterns observed in PLGA is extremely rare in ACC. PLGA is composed of cuboidal or columnar cells with vesicular nuclei and eosinophilic cytoplasm lacking basaloid features characteristic of ACC. The presence of angulated and hyperchromatic nuclei also helps in differentiating ACC from PLGA on biopsy

samples. Calcific deposits and cyst formation are more common in PLGA. The solid cellular areas of ACC are characterized by nuclear pleomorphism, increased mitotic activity, necrosis and tubular structures which are absent in PLGA. Perineural invasion is seen in both entities but PLGA exhibits a characteristic targetoid arrangement of perineural invasion[1,21].

Immunohistochemically, c-kit, a transmembrane receptor tyrosine kinase, aids in differentiating ACC from PLGA in challenging cases. Galectin-3 expression is observed in both PLGA and ACC and it has no role in the differentiation of ACC and PLGA[26,32].

Treatment and Prognosis

Wide surgical excision with adequate margins is the mainstay of treatment. Long term follow-up is required as late recurrences even after a decade from initial diagnosis may occur. The role of adjuvant radiotherapy is still not clear but it should be considered in cases with positive margins and advanced-stage disease[33]. The overall survival, prognosis and outcome of PLGA are excellent. In a recently published Danish study, the 5- and 10-year overall survival rates were 89% and 73%, respectively[33].

In a retrospective series of 24 patients by Seethala et al., 7 patients (29%) had a local recurrence. The loco-regional rate of recurrence was 33% with a median disease-free survival of 12.8 years. Four of 24 patients (17%) had lymph node metastases, 1 on presentation and 3 as regional recurrences [34]. Vincent et al. [5] reported a recurrence rate of 17% with a regional metastasis rate of 9%. In a literature review of 456 cases of PLGA by Kimple et al[35], and overall recurrence rate of 19% was identified. Fifty per cent of the recurrences occurred by 36 months; however, recurrences were reported up to 24 years after initial resection. Recurrence was seen in 13% of patients in a study of 73 patients of PLGA[33].

It is difficult to enumerate prognostic factors based on the rarity of this entity and the scarcity of literature. In a series by Seethala et al[34], the site was the only significant determinant of disease-free survival. Extrapalatal PLGAs of the base of the tongue and nasopharynx behave more aggressively. The patients with base of tongue lesions may present with cervical lymph node metastasis. Elective neck dissection must be performed even in a clinically node-negative patient with a PLGA of the base of the tongue. However, patients with a greater percentage of papillary component, positive margins, large perineural invasion and bone invasion had shorter disease-free survival but the differences were not statistically significant[34]. In a Danish study, perineural invasion significantly correlated with poorer overall survival, while free resection margins were associated with a significantly better recurrence-free survival[33].

Conclusion

PLGA is a low-grade salivary gland neoplasm with an indolent course. It primarily arises in minor salivary glands but can rarely occur in major salivary glands. It can be diagnostically challenging as it is characterized by morphological diversity between tumours and within the tumour. The treatment of choice is wide surgical excision with negative margins. The role of radiotherapy is still not established. Long term follow-up is necessary as late recurrences are known to occur.

Conflicts of interest: None

Funding support: None

References

1. McHugh JB, Visscher DW, Barnes EL. Update on selected salivary gland neoplasms. *Arch Pathol Lab Med* 2009;**133**:1763-74.
2. Freedman PD, Lumerman H. Lobular carcinoma of intraoral minor salivary gland origin: report of twelve cases. *Oral Surg Oral Med Oral Pathol* 1983; **56**:157-66.
3. Batsakis JG, Pinkston GR, Luna MA, Byers RM, Sciubba JJ, Tillery GW. Adenocarcinomas of the oral cavity: A clinicopathologic study of terminal duct carcinomas. *J Laryngol Otol* 1983; **97**:825-35.
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. Vincent SD, Hammond HL, Finkelstein MW. Clinical and therapeutic features of polymorphous low-grade adenocarcinoma. *Oral Surg Oral Med Oral Pathol* 1994; **77**:41-7.
6. 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.
7. 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.
8. Stenner M, Klussmann JP. Current update on established and novel biomarkers in salivary gland carcinoma pathology and the molecular pathways involved. *Eur Arch Otorhinolaryngol* 2009 Mar. **266**:333-41.
9. Tian Z, Li L, Wang L, Hu Y, Li J. Salivary gland neoplasms in oral and maxillofacial regions: a 23-year retrospective study of 6982 cases in an eastern Chinese population. *Int J Oral Maxillofac Surg.* 2010; **39**:235–242.
10. Shukla M, Gaud U, Kumar M, Pandey M. Polymorphous Low-Grade Adenocarcinoma (PLGA) in an 18-year-old male. *Indian J Surg* 2013; **75**:153-5.
11. Kumar M, Stivaros N, Barrett AW, Thomas GJ, Bounds G, Newman L. Polymorphous low-grade adenocarcinoma--a rare and aggressive entity in adolescence. *Br J Oral Maxillofac Surg* 2004; **42**:195-9.
12. Tsang YW, Tung Y, Chan JK. Polymorphous low-grade adenocarcinoma of the palate in a child. *J Laryngol Otol* 199;**105**:309-11.
13. Khosla D, Verma S, Gupta N, Punia RS, Kaur G, Pandey AK, et al. Polymorphous low-grade adenocarcinoma of the parotid in a teenager. *Iran J Otorhinolaryngol* 2017; **29**:299-302.
14. Pogodzinski MS, Sabri AN, Lewis JE, Olsen KD. Retrospective study and review of polymorphous low-grade adenocarcinoma. *Laryngoscope* 2006;**116**:2145-9.
15. Patel TD, Vazquez A, , Park RC, , Eloy JA. Polymorphous low-grade adenocarcinoma of the head and neck: A population-based study of 460 cases. *Laryngoscope* 2015;**125**:1644-9
16. 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.
17. Pelkey TJ, Mills SE. Histologic transformation of polymorphous low-grade adenocarcinoma of the salivary gland. *Am J Clin Pathol* 1999;**111**:785-91.
18. Mills SE, Garland TA, Allen MS Jr. Low-grade papillary adenocarcinoma of palatal salivary gland origin. *Am J Surg Pathol* 1984; **8**:367-74.
19. Lloreta J, Serrano S, Corominas JM, Ferrés-Padró E. Polymorphous low-grade adenocarcinoma arising in the nasal cavities with an associated undifferentiated carcinoma. *Ultrastruct Pathol* 1995;**19**:365-70.
20. 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.
21. Luna MA, Wenig BM. Polymorphous low-grade adenocarcinoma. In: Barners L, Everson JW, Reichert P, Sidrunsky D, editors. Pathology and genetics. Head and neck tumours. World health organization classification of tumours. *Lyon IARC press.* 2005;223-4.
22. Surya V, Tupkari JV, Joy T, Verma P. Histopathological spectrum of polymorphous low-grade adenocarcinoma. *J Oral Maxillofac Pathol* 2015;**19**:266.
23. Perez-Ordonez B, Linkov I, Huvos AG. Polymorphous low-grade adenocarcinoma of minor salivary glands: a study of 17 cases with emphasis on cell differentiation. *Histopathology* 1998;**32**:521-9.
24. Wenig BM, Harpaz N, DelBridge C. Polymorphous low-grade adenocarcinoma of seromucous glands of the nasopharynx. A report of a case and a discussion of the morphologic and immunohistochemical features. *Am J Clin Pathol* 1989; **92**:104-9.
25. , Sousa S, , Jaeger R, Loyola A, Crivelini M, al. Characterization of the cellular component of polymorphous low-grade adenocarcinoma by immunohistochemistry and electron microscopy. 1999; **35**:164-72.
26. Penner CR, Folpe AL, Budnick SD. C-kit expression distinguishes salivary gland adenoid cystic carcinoma from polymorphous low-grade adenocarcinoma. *Mod Pathol* 2002;**15**:687-91.
27. Ferrazzo KL, Alves SM Jr, Santos E, Martins MT, de Sousa SM. Galectin-3 immunoprofile in adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma of salivary glands. *Oral Oncol* 2007;**43**:580-5.
28. Regezi JA, Lloyd RV, Zarbo RJ, McClatchey KD. Minor salivary gland tumors: a histologic and immunohistochemical study. *Cancer* 1985;**55**:108-15.
29. Gnepp DR, Chen JC, Warren C. Polymorphous low-grade adenocarcinoma of minor salivary glands: an immunohistochemical and clinicopathologic study. *Am J Surg Pathol* 188;**12**:461-8.
30. Andersen C, Krutchkoff D, Pedersen C, Cartun R, Berman M. Polymorphous low-grade adenocarcinoma of minor salivary glands: a

clinicopathologic and comparative immunohistochemical study. *Modern Pathol* 1990;**3**:76-82.

31. Curran AE, White DK, Damm DD, Murrah VA. Polymorphous low-grade adenocarcinoma versus pleomorphic adenoma of minor salivary glands: the 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.
32. El-Nagdy S, Salama NM, Mourad MI. Immunohistochemical clue for the histological overlap of salivary adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma. *Interv Med Appl Sci* 2013; **5**:131-9.
33. Elhakim MT, Breinholt H, Godballe C, Andersen LJ, Primdahl H, Kristensen CA, et al. Polymorphous low-grade adenocarcinoma: A Danish national study. *Oral Oncol* 2016;**55**:6-10.
34. Seethala RR, Johnson JT, Barnes EL, Myers EN. Polymorphous low-grade adenocarcinoma: the University of Pittsburgh experience. *Arch Otolaryngol Head Neck Surg* 2010;**136**:385-92.
35. Kimple AJ, Austin GK, Shah RN, Welch CM, Funkhouser WK, Zanation AM, et al. Polymorphous low-grade adenocarcinoma: a case series and determination of recurrence. *Laryngoscope* 2014;**124**:2714-9.