An insight into diagnostically challenging salivary gland malignancy with case report: Polymorphous low grade adenocarcinoma

Amit Shah, Shilpa Patel, Jigna Pathak, Niharika Swain, Swenil Shah

Abstract

Polymorphous low-grade adenocarcinoma (PLGA) is difficult to diagnose due to its indolent clinical presentation and due to its morphological diversity that includes several microscopic patterns. Distinguishing it from high-grade tumors of salivary gland is important, as the management and prognosis of this tumor differ. We report a considerably rare case of PLGA in retromolar area highlighting various diagnostic challenges caused by the overlap of clinical and microscopic features between PLGA and other salivary gland neoplasms and discuss current management strategies.

Case Report

The present case report is about a 20-year-old male patient who reported with an asymptomatic swelling in his right retromolar region of about 4 months duration. On examination, a soft, smooth mass of about 2 cm × 1 cm in size was present in the right retromolar area. The soft-tissue mass was non-ulcerated, non-tender and was not fixed to underlying structures. There was no associated lymphadenopathy or sensory deficit. Hard tissue involvement was not present and was confirmed radiographically [Figure 1].

Considering the innocuous clinical presentation, excision of the lesion was performed. On histopathological examination, a well-circumscribed but unencapsulated lesion with infiltrative growth pattern was observed. Tumor consisted of polymorphous growth pattern in the center while characteristic Indian file pattern was present at the periphery. The individual cells were round to oval and spindled at places, with moderate cytoplasm and vesicular nuclei with prominent nucleoli and occasional mitosis. A small population of mucous like cells and clear cells were also evident. Connective tissue stroma was predominantly myxoid with delicate fibrous tissue. Lymphoid aggregates were observed in association with the tumor.

Introduction

The present term, polymorphous low-grade adenocarcinoma (PLGA) was first described by Evans and Batsakis in 1984 and has replaced various previously described terms like lobular carcinoma described by Freedman and Lumerman in 1983 and terminal duct carcinoma described by Batsakis et al. in 1983.[1‑3] World Health Organization in their 1991 classification of salivary gland tumors considers PLGA as separate entity and included tumors which were previously misdiagnosed as pleomorphic adenomas (PAs), monomorphic adenomas, malignant PAs, adenoid cystic carcinomas (AdCCs) or adenocarcinoma not otherwise specified.[4,5] Almost exclusive to minor salivary glands, PLGA affects palate most frequently and accounts for about 60% of all PLGAs. Buccal and labial mucosa, alveolar mucosa, retromolar trigone, tongue, floor of mouth and parotid gland are other sites of occurrence in that order.[6,7] Uncommon locations include lacrimal glands, nasopharynx, nasal cavity, tonsillar region and paranasal sinuses.[5‑7] We present a rare case of PLGA of retromolar area highlighting various diagnostic challenges caused by the overlap of clinical and microscopic features between PLGA and other salivary gland neoplasms and discuss current management strategies.

Key words: High-grade tumors, polymorphous low-grade adenocarcinoma, retromolar area, salivary gland neoplasms
Considering the histopathological features, a diagnosis of PLGA was made [Figure 2]. Initially, the innocuous history of the lesion did not prompt extensive systemic investigation which was subsequently performed and found to be negative. No sign of recurrence was observed on 1 year follow-up, patient is now under close follow-up.

**Discussion**

PLGA is a low grade malignancy of salivary glands which develops from intercalated (terminal) duct cells. The indolent, asymptomatic and benign looking neoplasm is frequently diagnosed late in 5-7th decade and affects females more frequently in ratio 2:1.[5,7] PLGA represents 2nd most common intra-oral malignant salivary gland neoplasm.[9] This considerably common neoplasm, in our case showed uncommon and rare presentation in 20 years, male patient. Furthermore, neoplasm affected minor salivary gland in retromolar area which accounts for only 0.5% of all cases of PLGA.[9]

PLGA, histopathologically, is characterized by a triad of infiltrative growth, multiple architectural growth patterns (hence the term polymorphous) and cytologic uniformity.[9] On microscopic examination, characteristic polymorphous growth patterns including solid, trabecular, glandular, cribriform, fascicular, tubular and papillary are evident. In general, the central portion consists of the more solid growth patterns, with the glandular and tubular elements seen more often at the infiltrative periphery.[9] Tubular structures are lined by a single cell layer and resemble terminal ducts.[10] Cells often assume a linear, single-cell arrangement at the tumor periphery known as “Indian file” or “beads on a string” pattern of infiltration.[10,11] Necrosis is, at most, extremely rare and mitotic figures are infrequent and never atypical. PLGA invades nerves in about 30% of cases, often in a so-called targetoid arrangement, with cords of cells concentrically arranged around nerves.[2] Tumor cells are uniform and isometric; they have vesicular nuclei with pale eosinophilic cytoplasm, which seems to be washed out in appearance.[9,12] The diagnosis of PLGA may pose difficulty due to histopathological overlap with other salivary gland neoplasms. Multiple histomorphologic patterns and cytologic uniformity are features similar to those seen in AdCC and PA. Differentiating between PLGA, AdCC and PA is a diagnostic challenge especially in small biopsy sample.[13] Hence, recognition of subtle differences in histology between PLGA and other salivary gland neoplasms are critical in avoiding misdiagnosis and ultimately improper management.

AdCC resembles PLGA in age, gender and palatal predilection, perineural invasion as well as slow rate of growth, variability of growth patterns and infiltrative borders. In contrast, dull pain in an ulcerated lesion is a frequent complaint with AdCC which is more aggressive neoplasm with greater potential of metastasis. Histopathologically, like PLGA, AdCC can be architecturally heterogeneous, but double-layered ductal

**Figure 1:** Clinical photograph showing intraoral swelling in right retromolar region with normal appearing overlying mucosa (a) Orthopantogram showed no associated bone involvement (b)

**Figure 2:** Polymorphous growth pattern with tumor cells arranged in characteristic Indian file pattern at the periphery (a, H and E, ×100) and solid (b, H and E, ×100), trabecular and tubular at the center of the lesion. Few mitotic figures and minor cellular atypia was present. Tumor cells were mostly cuboidal and at places were spindled (c, H and E, ×400), clear (d, H and E, ×400) and mucous-like (e, H and E, ×400). Tumor-associated lymphoid aggregates observed (f, H and E, ×100). An infiltrative growth pattern was evident, with tumor islands infiltrating perivascular region (g, H and E, ×100), overlying epithelium (a, H and E, ×100) and adjacent normal minor salivary gland (h, H and E, ×100)
lining and preponderance of cribriform pattern throughout the tumor is suggestive of AdCC. Cells in PLGA are cuboidal or columnar. They have vesicular nuclei and often conspicuous eosinophilic cytoplasm without the basaloid features characteristic of AdCC. Although recognition of nuclear atypia (hyperchromatic and angulated) is supportive of AdCC; presence of calcific deposits, typical targetoid perineural invasion and papillary growth favors PLGA rather than AdCC. Furthermore, the solid cellular areas of PLGA lack nuclear pleomorphism, necrosis, increased mitotic activity and the numerous tubular structures characteristic of the solid variant of AdCC. Immunohistochemistry is not extremely helpful in differentiating AdCC and PLGA. Conflicting data on role of certain markers including S100, vimentin, cytokeratins, c-kit and glial fibrillary acidic protein have been published. However, proliferative markers can be used supportively to establish a diagnosis. Usually, the proliferative index in PLGA is <5%, whereas in AdCC it is usually >20%.

PLGA and PA affecting minor salivary glands, share some common clinical features like absence of symptoms (pain and paraesthesia), slow growth, smooth texture and palatal predilection except metastasis which sometimes may occur in PLGA but never in PA. Histopathologically, PA of minor salivary glands may not be encapsulated but lack infiltrative pattern and are well circumscribed. Unlike PLGAs, PAs are characterized by bilayered ductal or gland like structures present in characteristic chondromyxoid stroma. Both content and architectural arrangement of cellular and stromal elements contributes to the morphological diversity, a well-known hallmark of PA. Conversely, if perineural invasion is present, PA can be ruled out. In cases posing a diagnostic dilemma based on histopathology, immunohistochemistry can be performed. PA, characteristically are positive for myoepithelial cells unlike PLGA, which may only show faint and patchy reactivity in luminal cells.

A distinction should also be made between PLGA and low-grade papillary adenocarcinoma (LGPA) because the latter displays a more aggressive behavior; their rates of both local recurrence and regional lymph node metastasis are higher. Most of the authors agree that if the histological features are predominantly papillary, the tumor should be identified as LGPA. Complete wide surgical excision is the treatment of choice for PLGA which has not metastasized. Uncommonly, post-operative radiation therapy has been suggested for recalcitrant recurrences, but it appears to be palliative rather than curative. The overall survival for PLGA is generally excellent with conservative management, with more than 95% of patients alive after a mean follow-up of 10 years. Although, PLGA is characterized by favorable prognosis, sporadic reports of local or distant metastasis as well as transformation to a higher grade adenocarcinoma, sometimes culminating in death, are cited in the literature. It has also been suggested that extra palatal salivary gland carcinomas appear to behave in a more aggressive fashion than those of the palate. These observations confirm the true malignant nature of this indolent neoplasm and highlight the significance of timely detection and management to prevent potential deadly or morbid sequel. Patient, in present case reported after 4 months of initial appearance of the lesion which helped in early diagnosis, treatment with minimal morbidity and better prognosis of this “benign appearing” malignant neoplasm.

Conclusion

PLGA is a well-defined entity in the minor salivary glands. Its occurrence in the retromolar area is rare with very few cases reported in the literature. Diagnosis of this “benign-appearing” malignant neoplasm remains challenging both clinically and histopathologically. Hence, clinically innocuous appearing neoplasms of salivary gland of extra palatal origin should be assessed with caution.

References


Source of Support: Nil.  Conflict of Interest: No conflict of interest.