REVIEW ARTICLE

POLYMORPHOUS LOW GRADE ADENOCARCINOMA OF THE PAROTID GLAND. CYTOLOGICAL, HISTOLOGICAL AND IMMUNOHISTOCHEMICAL FEATURES AND REVIEW OF THE LITERATURE

Demetrio Tamiolakis[1], Vasilios Thomaidis[2], Ioannis Tsamis[2], Eleni Kariki[3], Athanasia Kotini[4], Maria Lambropoulou[5], Panagiotis Boglou[5], Nikolaos Papadopoulos[5]

General Hospital of Alexandroupolis, Greece: Department of Cytology[1], Department of Maxillofacial Surgery[2]; Papanicolaou Hospital of Salonica, Greece: Department of Pathology[3]; Democritus University of Thrace, Greece: Department of Medical Physics[4], Department of Histology – Embryology[5]

Summary: Aim: Polymorphous low grade adenocarcinoma of the salivary glands (PLGA) is a low grade neoplasm that predominantly occurs in the minor salivary glands. In this site is amenable to biopsy and histologic diagnosis. However, experience with cytological findings in these tumors is limited. We describe the cytology of this entity. Experimental design: Touch imprint cytology of a primary parotid PLGA is specified and correlated with histology. Results: Smears were hypercellular showing branching papillae, sheets and clusters of uniform cells with bland nuclei, dispersed chromatin and no nucleoli. The cells had a scant to moderate amount of eosinophilic cytoplasm. They formed tubular structures containing hyaline globules. Conclusions. The cytologic differential diagnosis of PLGA includes adenoid cystic carcinoma, pleomorphic adenoma, and monomorphic adenoma. PLGA should be considered in the differential diagnosis of head and neck tumors, where the cytology suggests on of the above mentioned tumors, even when the clinical findings (involvement of a major salivary gland, lymph node metastasis) is not typical of PLGA.

Key words: *PLGA; Salivary gland tumors; Cytology; Histology; Immunohistochemistry*

Introduction

Polymorphous low grade adenocarcinoma is a tumor of limited malignancy involving predominantly minor salivary glands, particularly of the palate, where it represents the second most frequent malignant tumor (3,7,8). There are occasional reports of involvement of major salivary glands, including the parotid gland (10,12,14,15,19). Its behavior is indolent, with a 10–15% rate of local recurrence, a regional lymph node metastasis rate of approximately 10%, and rare reports of distant spread (23,24). These tumors are characterized by architectural diversity and cytologic uniformity. The nuclei are oval to spindled with fine chromatin and inconspicuous nucleoli. A moderate amount of eosinophilic cytoplasm is characteristic, and mitoses and necrosis are rare. Tubular, cribriform, papillary, solid, and fascicular areas alternate within the tumor and an infiltrative margin with perineural invasion is often seen. A myxoid, hyaline, or myxohyaline stroma is always seen and often forms intratubular globules (20,21,26). The histologic differential diagnosis includes adenoid cystic carcinoma and pleomorphic and monomorphic adenomas.

Experience with the cytology of this tumor is limited to occasional case reports (5,9). This tumor is increasingly being recognized histologically; and with the routine use of FNAC in the evaluation of head and neck lesions, this tumor is expandingly in the scope of the cytopathologist. This is of particular relevance when the tumor presents in an atypical fashion, either as a metastasis or rarely in a major salivary gland.

This study was undertaken to assess the value of imprint cytology in the diagnosis of PLGA and highlight the pitfalls and dilemmas.

Study design

A case of PGLA arising in the right parotid gland region of a 65-year old woman with both imprint cytology and histologic confirmation, was retrieved from the surgical pathology and cytopathology files of the Papanicolaou Hospital of Salonica, and Regional Hospital of Alexandroupolis.

Cytologic material was obtained by touch imprint smearing. Air-dried smears were stained with the Hemacolor ra-

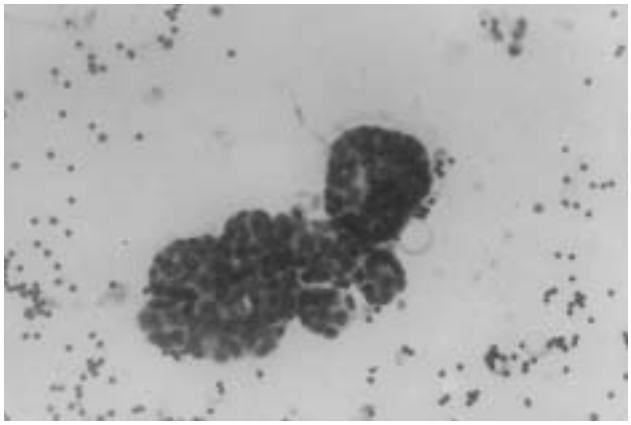

Fig. 1: PLGA, touch imprint cytology: Papillary clustering of tumor cells, PAPX200.

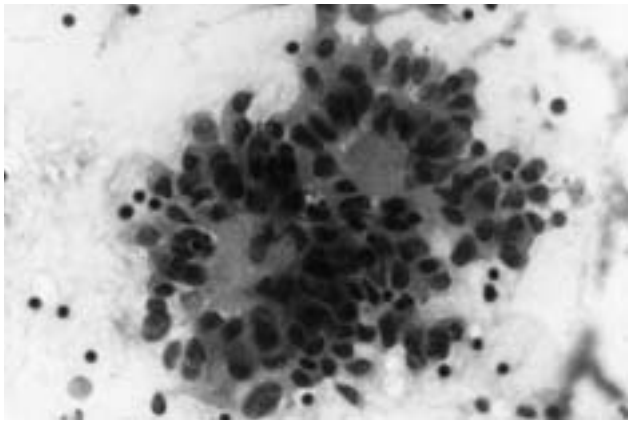

Fig. 2: PLGA, touch imprint cytology: Hyaline globules within the clusters of tumor cells, PAPX400.

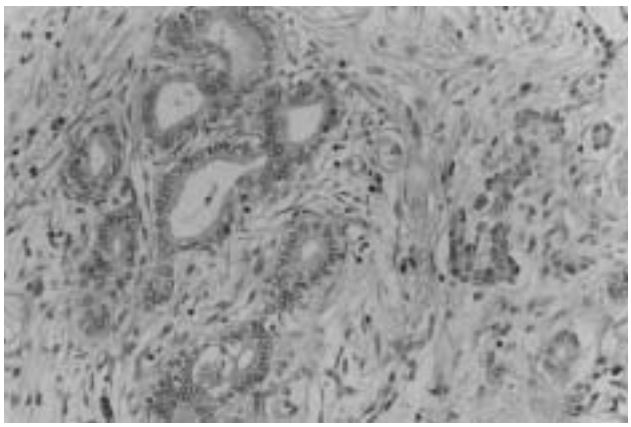

Fig. 3: PLGA, tissue section. Polymorphous architectural patterns of tumor cells, H&EX200.

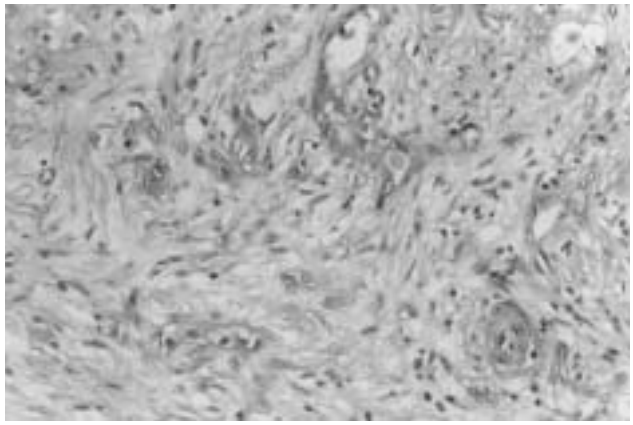

Fig. 4: PLGA, tissue section. Myxohyaline matrix in the background of the tumor cells. H&EX200.

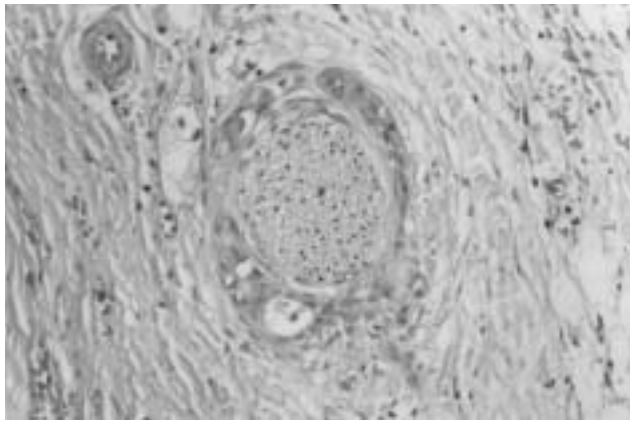

Fig. 5: PLGA, tissue section. Perineural invasion by tumor cells. H&EX200.

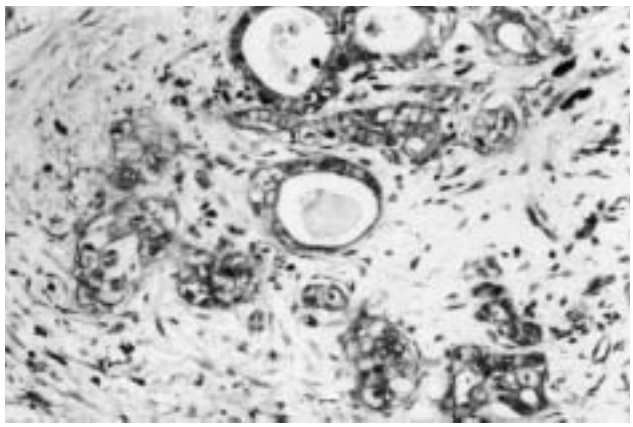

Fig. 6: PLGA, tissue section. Tumor cells showing a strong reactivity with 34βE12 cytokeratin Immunostain X200.

pid method, and smears fixed with cytospray were stained with the Papanicolaou technique. Histologic specimen was fixed in 10% neutral buffered formalin, and paraffin embedded. Sections were cut at 5 μm and stained with hematoxylin and eosin.

Results

Cytology: Touch imprint smears were hypercellular, consisting of branching papillary clusters (Fig. 1) and sheets of bland, uniform cells with round-to-oval, focally spindled nuclei; dispersed chromatin; and absent or inconspicuous nucleoli. Intranuclear inclusions were frequently seen. There was a scant-to-moderate amount of eosinophilic cytoplasm. Some cells demonstrated basaloid features, whereas admixed cells showed moderately abundant eosinophilic cytoplasm. Mitoses and pleomorphism were absent. A characteristic feature was the presence of abundant hyaline globules within glandlike spaces in the clusters of cells, similar to the globules of adenoid cystic carcinoma (Fig. 2).

Histology: The tumor was generally poorly circumscribed, with infiltrative margins, and had a polymorphous architecture showing predominantly tubular, cribriform, solid, and papillary patterns with transitions from one pattern to the next within tumor (Fig. 3). A dispersed myxohyaline matrix was seen between the neoplastic cells (Fig. 4). Mitoses and pleomorphism were not seen, but perineural invasion was clearly identified (Fig. 5).

Immunohistochemical control: A panel of monoclonal antibodies including cytokeratins (CAM5.2 and 34βE12), CEA, EMA, Vimentin, S-100, SMA (smooth muscle actin), GFAP (glial fibrillary acidic protein) and Bcl-2 was employed. The neoplastic cells showed a moderate to strong reactivity with cytokeratins CAM5.2 and 34βE12 (Fig. 6), EMA, Vimentin, S-100, SMA, and Bcl-2. A negative reaction with CEA and GFAP was observed.

Discussion

Polymorphous low grade adenocarcinoma is an architecturally polymorphous tumor with papillary, cribriform, tubular, solid, and fascicular areas present in varying proportions in each tumor (3,7,8). In contrast to the architectural heterogeneity, the cytology is uniform with little variation in nuclei, no pleomorphism, and rare mitoses. Hyaline globules within the glandular spaces are often seen, as is myxohyaline stroma. The tumor behaves in a low grade fashion as the name suggests, with a 10–15% local recurrence rate, a metastatic rate of approximately 10%, and rare distant spread (20,23,24,26). The histologic differential diagnosis includes pleomorphic adenoma, which can be distinguished by its well-circumscribed nature and its biphasic combination of epithelial cells and matrix. Adenoid cystic carcinoma can be distinguished by its characteristic hyperchromatic basaloid cells with scant cytoplasm and without spindling, in contrast to the cuboidal oval-to-round cells of PLGA, which have dispersed chromatin and moderate amounts of eosinophilic cytoplasm. The infiltrative borders of the PLGA helps them to be distinguished from monomorhic adenomas, such as trabecular and canalicular adenomas.

An understanding of the morphogenesis of PLGA is necessary to facilitate the recognition and diagnosis of these tumors. The architectural and cytologic diversity noted in PLGA is not uncommon in salivary gland neoplasms (6) and its morphogenesis and cellular differentiation appears to be a process similar to the one seen in pleomorphic adenoma and other salivary gland tumors (6). As in pleomorphic adenoma, PLGA is composed of luminal and nonluminal cells, which according to their relative proportions and distribution differentiate into a variety of morphological patterns. A predominance of luminal cells gives rise to tubules and duct-like structures; whereas increased numbers of nonluminal cells in relation to luminal cells are responsible for the development of solid cords and trabeculae. A predominance of nonluminal cells translates into solid nests and cribriform areas with pseudoluminal spaces. This relation of cellular differentiation and morphological heterogeneity in PLGA had been investigated by Norberg et al. (16) who also found luminal, basal and myoepithelial differentiation in three cases studied by immunohistochemistry and electron microscopy.

Given these morphogenetic similarities, it is easy to understand the difficulties in separating PLGA from pleomorphic adenoma and adenoid cystic carcinoma. In many areas and at the cytological level it is often difficult if not impossible to distinguish PLGA from pleomorphic adenoma. The most useful features in distinguishing these two neoplasms are the lack of tubules with two cell layers or squamous differentiation, lobules of cartilage and GFAP immunostaining in PLGA. Furthermore, perineural or stromal invasion is not seen in pleomorphic adenoma. This distinction may prove to be difficult or impossible in small biopsies or cytological aspirates and the possibility of a PLGA should be excluded when examining minor salivary gland tumors with the features of a pleomorphic adenoma. Adenoid cystic carcinoma is composed of cells with a more basaloid appearance, higher nucleocytoplasmic ratio, and more hyperchromatic nuclei than the luminal and nonluminal cells of PLGA; in addition, the tubules and ducts of adenoid cystic carcinoma reveal a two cell lining and have more extensive perineural and stromal invasion.

The presence of papillary areas in PGLA was initially described by Evans and Batsakis (7) and confirmed by others (13,22,25). However, the inclusion of papillary neoplasms within the morphological spectrum of PLGA remains controversial. There have been suggestions of separating PLGA into two groups: low-grade papillary adenocarcinoma and nonpapillary adenocarcinoma (terminal duct) carcinoma largely due to the more aggressive behavior of the former (4).

The immunohistochemical features of PLGA also support the presence of luminal and nonluminal cell types. As

in previous studies (11,18,22) our case showed staining for keratins (low and high molecular weight), vimentin and S-100. Two previous studies found staining in PLGA for HMWK: Gnepp et al. (11) described immunoreactivity both in luminal and nonluminal cells, whereas Regezi et al. (18) did not specify its distribution. Positive immunostaining for EMA has also been described in luminal and nonluminal cells of PLGA (11,22). Most studies (2,16,22) indicate that expression of CEA in PLGA is infrequent and limited to luminal cells and our results are in agreement with these findings. Our study also demonstrated a total absence of GFAP. Regezi et al. (18) identified in a series of 16 cases, one positive for GFAP and similar results have been reported in smaller studies (2,11,16). Bcl-2 gene product expression has been demonstrated in basal cells of the striated and excretory ducts in normal salivary gland, basal cells adenoma, nonluminal cells in pleomorphic adenoma and in some acinic cell carcinomas (1,17). Anti-bcl-2 stained luminal and nonluminal cells in our case, thus differing from its previously reported distribution in pleomorphic adenoma (17). Overexpression of bcl-2 suggest that inhibition of programmed cell death plays a significant role in the pathogenesis of PLGA and may help explain their indolent behavior.

Polymorphous low grade adenocarcinoma, should be kept in mind when evaluating cytologic preparations from this region because diagnosis of this tumor by cytopathology is difficult. It has been well established that diagnosis of this entity improves with the awareness and experience of the cytopathologist.

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Nikolaos Papadopoulos
Assoc. Professor, Democritus University of Thrace,
Dragana, 68 100 Alexandroupolis, Greece.
e-mail: npapad@med.duth.gr