Low-Grade Clear Cell Carcinoma with Myoepithelial Features in the Submandibular Gland

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Abstract Clear cell carcinoma is rarely found in the salivary gland. It is classified as a low-grade carcinoma. This case demonstrates a low-grade clear cell carcinoma with myoepithelial features in the submandibular gland which differs from hyalinizing clear cell carcinoma and epithelial-myoepithelial carcinoma. A 32-year-old man presented with a 7 month history of left submandibular swelling. Left submandibular gland excision and left-sided supra-omohyoid neck dissection were performed. Microscopically, the tumor was circumscribed and composed predominantly of cords and nests of clear ovoid cells, set in a densely hyalinizing stroma. These cells are diffusely immunoreactive for cytokeratin AE1/AE3 and focally reactive for vimentin and smooth muscle actin (SMA). Based on these findings, the tumor was diagnosed as “a low-grade clear cell carcinoma with myoepithelial features”. The post-operative course was uneventful and the patient is free from disease 21 month after surgery.

Keywords Clear cell carcinoma · Myoepithelial carcinoma · Salivary gland · Hyalinizing clear cell carcinoma · Epithelial-myoepithelial carcinoma

Introduction

Clear cell carcinoma of the salivary gland is one of the rarest tumors and is classified as a low-grade carcinoma. However, this type of tumor was previously misclassified as

other types of tumors containing clear cells such as muco-epidermoid carcinoma, epithelial-myoepithelial carcinoma, and adenocarcinoma not otherwise specified [1–3]. Histologically clear cell carcinomas can be divided into two subtypes. The first type is the biphasic epithelial-myoepithelial carcinoma. The second type is the monophasic myoepithelial carcinoma. Recently, a hyalinizing clear cell carcinoma which is a low-grade indolent and rare salivary gland tumor was described by Milchgrub et al. in 1994 [4].

This case report documents a rare case of a low-grade clear cell carcinoma with myoepithelial features in the submandibular gland which differs from hyalinizing clear cell carcinoma and epithelial-myoepithelial carcinoma.

Case Report

A 32-year-old man who had a submandibular swelling on the left side of 7 months duration was referred to this clinic on 31 March, 2005. His past and family histories were unremarkable. On physical examination a smooth, elastic, nontender, 3 cm mass was detected in the left submandibular gland. Neither facial paralysis nor swelling of cervical lymph nodes was observed. Computed tomography of the neck with iodate contrast revealed an approximately 2 cm diameter mass in the left submandibular gland which showed a hypointensity area without marked enhancement (Fig. 1). Observation of the fine needle aspiration cytology revealed class III (borderline) malignancy. The patient was clinically diagnosed with a left-sided submandibular gland tumor. The tumor was removed, including the left submandibular gland and a left-sided supra-omohyoid neck dissection was performed under general anesthesia on 27 May, 2005. A histopathological examination of frozen sections of the tumor, observed during the operation suggested a low grade malignancy.

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Macroscopically the tumor measured $2.3 \times 2.3 \times 1.5$ cm. Its cross-section was homogeneous and milky-white in color. Microscopically, the tumor was circumscribed and composed of cords and nests of clear ovoid cells predominantly, set in a densely hyalinizing stroma (Fig. 2a). The tumor cells exhibited moderate nuclear atypia and were somewhat angulated or convoluted. Mitotic figures were inconspicuous. These cells were diffusely immunoreactive for cytokeratin AE1/AE3 and focally reactive for vimentin and smooth muscle actin (SMA) (Fig. 2b, c). Weak staining with S100 was observed (Fig. 2d). The MIB1 labeling index was about 10% (Fig. 2e). Both the histopathologic and immunophenotypic features of this tumor support the interpretation of a low-grade clear cell tumor, with a limited degree of myoepithelial differentiation. On the basis of these findings, the tumor was diagnosed as “a low-grade clear cell carcinoma with myoepithelial features”. No additional treatment was given to the patient because both the surgical margin and cervical lymph nodes were histologically negative for tumor cells. The patient is currently free from disease at 21 months after surgery.

Fig. 1 Computed tomography of the neck with iodate contrast revealed a mass measuring approximately 2 cm in diameter in the left submandibular gland which showed a hypointensity area without any marked enhancement

Discussion

Clear cell carcinoma (CCC) is a malignant neoplastic tumor observed in approximately 1% of all salivary gland tumors [5]. CCC is now recognized as a distinct tumor species, although it had previously designated as glycogen-rich adenoma, glycogen-rich adenocarcinoma, clear cell myoepithelioma, adenomyoepithelioma, and epithelial–myoepithelial carcinoma of the intercalated ducts [1–3, 5–7]. Clear cells are observed as a component of numerous benign and malignant salivary gland tumors, so this type of clear cell carcinoma in the salivary gland has been reported under various names.

Chen [8] morphologically classified clear cell carcinomas into two subtypes. The first subtype is a bimorphic variant composed of tubules lined by an inner layer of eosinophilic cells and an outer layer of clear cells with a double-layered arrangement known as an epithelial–myoepithelial carcinoma. These tumors are of intercalated duct origin and are usually associated with the major salivary glands.

The second type is the monomorphic variant composed entirely of clear cells, usually associated with the minor salivary glands. Milchgrub et al. [4] determined that these were distinctive salivary tumors known as hyalinizing clear cell carcinoma.

In the present case, the differential diagnosis, considered both hyalinizing clear cell carcinoma and epithelial–myoepithelial carcinoma.

Epithelial–myoepithelial carcinoma differs from other clear cell carcinomas by the formation of biphasic tumors with ductal formation. They are composed of islands of large solid nests or sheets of tumor cells, which are lined by cuboidal to columnar epithelium. Both the proportion and arrangement of the biphasic components to the sheets of clear cells are quite variable. Occasionally, the clear cell component may predominate and the biphasic component may be focal [9]. Immunohistochemistry, myoepithelial antigens (S-100 protein, smooth muscle actin, muscle specific actin, and vimentin) are expressed in epithelial–myoepithelial carcinoma [5, 9, 10]. The observation of these markers is characteristic of myoepithelial differentiation.

In the present case tumor cells were immunoreactive for cytokeratin AE1/AE3 diffusely and for vimentin and smooth muscle actin (SMA). They showed no focal staining for S100.

Electron microscopical observations revealed the tumor cells to have epithelial features (Fig. 3). Tonofilaments and junctional complexes were clearly observed between the tumor cells.

Based on these observations, hyalinizing clear cell carcinoma was considered. In general hyalinizing clear cell carcinoma is composed of cords, nests and trabeculae of glycogen-rich clear cells and eosinophilic cells surrounding

Fig. 2 The histopathological and immunohistological findings either a solid nest or trabecula of the tumor cells are set in the hyalinizing fibrous stroma. The tumor cells possess clear cytoplasm and either round or oval nuclear with moderate atypia ($\times 200$) (a). Cytokeratin staining is positive ($\times 200$) (b). Focal smooth actin (SMA) staining is seen ($\times 100$) (c). In addition, a weak S100 expression is seen ($\times 200$) (d). The mib-1 index is about 10% ($\times 100$) (e)

by a hyalinizing stroma [11]. Immunohistochemically, the tumor cells are of epithelial origin without myoepithelial differentiation [4, 9]. Demonstration of CK positivity and the absence of S100 and SMA are necessary to diagnose HCCC [4, 6, 12, 13]. But the vimentin and SMA staining was different in the present case.

Polymorphous low grade adenocarcinoma was also considered. In general, it would be an uncommon finding in the submandibular gland and these tumors do not exhibit the degree of nuclear atypia observed in the present case.

The final diagnosis was a low-grade clear cell carcinoma with myoepithelial features. Most tumors with a major clear cell component are classified as tumors with low-grade malignancy and the incidence of metastasis or local recurrence is low [1, 3, 5]. In the present case, both the surgical margin and cervical lymph nodes were pathologically tumor-free, so post-operative radiotherapy was not considered. The patient was followed up for 21 month post

Fig. 3 Electromicroscopical findings ($\times 18,000$) Tonofilaments are observed on the *left side* of the picture. Junctional complexes are confirmed to exist between the tumor cells

operatively and there were no recurrence and no metastasis. However, both the youth and relatively high MIB1 index value (~10%) observed in this patient indicate that an intensive and long-term follow-up is required.

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