Mucous and Ciliated Cells in Oral Lesions: Potential Pitfall of Additional Two Cases

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1. Abstract

A 47-year-old Japanese male had a radicular cyst at the upper right first molar. Histologically, the lesion had a cystic wall comprising fibrous tissue lined by ordinary non-keratinized stratified squamous cells; however, the luminal surface was extensively replaced by columnar mucous cells and the superficial layer showed numerous cilia.

A 16-year-old female had low-grade mucoepidermoid carcinoma at the base of the tongue. The tumor was 1.5 cm in size; presented a solid, relatively well-defined mass; histologically formed large and small nests adjacent to the minor salivary glands and skeletal muscle; and was accompanied by glandular cavities or cysts. A limited portion of the cystic structure had numerous cilia on the luminal surface. Mucous cells were immunoreactive for MUC1, MU4, and MUC5AC. Fluorescent in situ hybridization for MAML2 revealed obvious split signals.

These two cases were added to discuss the diagnostic problems with mucous cells and ciliated epithelium in connection with the previous report.

To the Editor,

In our previous report, we described a case of dentigerous cyst with marked mucous cell metaplasia requiring differentiation from mucoepidermoid carcinoma as a result, which also included ciliated epithelium [1]. Here, we added two more cases to discuss the diagnostic problems with mucous cells and ciliated epithelium.

The first case was a 47-year-old Japanese male who had a radicular cyst at the upper right first molar characterized by gingival swelling and mild tenderness for a year. X-ray pantomograph and intraoperative findings revealed obvious continuity between the cyst and the apex of the first molar.

Histologically, the lesion had a cystic wall comprising fibrous tissue lined by ordinary non-keratinized stratified squamous cells; however, the luminal surface was extensively replaced by columnar mucous cells, and the superficial layer had numerous cilia (Figure 1a, b). Squamous cells having definite intercellular bridges remained in the basal polar (Figure 1c). Mucous cells were positive for periodic acid–Schiff (PAS), alcin blue, and mucicarmine stains (Figure 1d–f). Large peripheral nerve fiber bundles, muscular blood vessels, or ectopic tissues were not detected within the cystic wall.

Immunohistochemically, the entire epithelium was positive for AE1/AE3, CAM5.2 for mucous cells, and 34βE12 for squamous cells (Figure 1g–i). MUC family expression was identical to that of the previous report: the mucous cells were positive for MUC1, MU4, and MUC5AC (Figure 1j–l) and negative for MUC2 and MUC6.
**Figure 1:** Case 1. Lesion showing a cystic wall comprising fibrous tissue; the luminal surface has been extensively replaced by columnar mucous cells (a), and the superficial layer shows numerous cilia (b). Squamous cells having definite intercellular bridges remaining in the basal polar (c). Mucous cells are positive for PAS (d), alcian blue (e), and mucicarmine stains (f). The entire epithelium is positive for AE1/AE3 (g), CAM5.2 for mucous cells (h), and 34βE12 for squamous cells (i). Mucous cells are positive for MUC1 (j), MUC4 (k) and MUC5AC (l).
As well as dentigerous cyst, radicular cyst is one of typical odontogenic cysts. Although metaplastic changes involving mucous cells and ciliated epithelium are generally rare in odontogenic cysts, histological alterations in such cases could be extremely drastic and even confusing [1]; thus, it may interfere with accurate diagnosis. A mixture of large numbers of ciliated epithelium could lead to a misdiagnosis of a group of non-odontogenic developmental cysts, formerly known as facial fissural cysts [2]; however, many of them are generally considered inappropriate and have been removed from general histological classification [3,4]. Nasopalatine duct cyst is the most common non-odontogenic developmental cyst and closely resembled the first case in terms of histology, but occurs only in the midline of the maxilla [4,5]. Moreover, thyroglossal duct cysts closely resemble this case, but they usually contain ectopic thyroid tissues and occur in the soft tissues below the tongue [4]. In such cases, information regarding the lesion location and its association with the teeth is essential for accurate diagnosis, and pathologists may need to make efforts to extract accurate information from the clinician depending on the case.

The second case was a 16-year-old girl with low-grade mucoepidermoid carcinoma at the base of the tongue. After experiencing throat discomfort for about a year, she visited a regional general hospital and underwent surgical resection of the lesion. The tumor was 1.5 cm in size; presented a solid, relatively well-defined mass; histologically formed large and small nests adjacent to the minor salivary glands and skeletal muscle; and was accompanied by glandular cavities or cysts containing eosinophilic mucus fluid (Figure 2a). The tumor mainly comprised polygonal and ovoid cells with slight nuclear atypia and scarce keratinization (Figure 2b) along with a small number of clear and columnar cells. The limited portion of the cystic structure had a large number of cilia on the luminal surface (Figure 2c). Although glandular features were predominantly detected throughout, 34βE12, CK5/6, p40, and p63 were partially positive (Figure 2d–f) and a few oncocytic cells were highlighted with mitochondria immunohistochemically. The labeling index on p53 and Ki-67 was low overall. Following the report by Sato et al. [6], fluorescent in situ hybridization (FISH) for MAML2 was performed in the same laboratory using the same procedure, and split signals were confirmed (Figure 2g, h).
Figure 2: Case 2. Tumor forming large and small nests adjacent to the minor salivary glands and skeletal muscle (a) and accompanied by glandular cavities or cysts containing eosinophilic mucus fluid (b). The limited portion of the cystic structure has a large number of cilia on the luminal surface (c). 34βE12 (d), CK5/6 (e), and p63 (f) are partially positive, suggesting squamous or intermediate cells. FISH for MAML2 showing clear split signals (g,h).

In general, combination of squamous and mucous cells tends to erroneously lead to the diagnosis of mucoepidermoid carcinoma, however it is not so a simple tumor, because it includes a wide variety of cellular populations.

As to the present case, although the diagnosis of mucoepidermoid carcinoma itself was possible without FISH, it has been a question for us whether or not mucoepidermoid carcinoma could have cilia over years even after the diagnosis was confirmed. However, the diagnosis is made more reliable by utilizing FISH for MAML2, which is regarded a useful tool for confirming the diagnosis of mucoepidermoid carcinoma [6], and in recent years, extremely rare cases associated with ciliated cells have been described in the English literature [7,8]. Thus, our doubt has also been resolved. In our previous report, a case requiring differentiation from mucoepidermoid carcinoma was described, but the existence of ciliated epithelium was not mentioned as a clue for differentiation because this fact was already known to the authors.

Finally, further commentary should be added to the previous case, and it should be emphasized that the presence itself of ciliated cells does not interfere with the diagnosis of mucoepidermoid carcinoma.

In addition, data on primary antibodies used for immunohistochemistry in the present cases were noted as follows; AE1/AE3 (clone PCK26, Ventana Medical System, USA), CAM5.2 (clone CAM5.2, Ventana Medical System, USA), 34βE12 (clone 34βE12, Ventana Medical System, USA), CK5/6 (clone D516 B4, Dako, Denmark), p40 (clone BC28, Ventana Medical System, USA), p63 (clone 4A4, Ventana Medical System, USA), mitochondria (clone AE1, Biogenesis, UK), p53 (clone DO-7, Ventana Medical Systems, USA), Ki-67 (clone MIB-1, Dako, Denmark), MUC1 (clone H23, Ventana Medical System, USA), MUC2 (clone MRQ-18, Sigma-Aldrich Co, USA), MUC4 (clone EPR9308, abcam, USA), MUC5AC (clone MRQ-19, Sigma-Aldrich Co, USA), and MUC6 (clone MRQ-20, Sigma-Aldrich Co, USA).

FISH for the MAML2 was performed as per the report by Sato et al. [2] using the ZytoLight SPEC MAML2 Dual Color Break Apart Probe (ZytoVision, Bremerhaven, Germany).

2. Acknowledgement

Figures 2c, 2g, and 2h were obtained from our own publication by Harada H and Kawahara A (2018) entitled “Salivary gland tumors: practical learning with consultation cases” in courtesy of Medical View Co Ltd. The usage was kindly permitted by the publisher.
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