≪Case Report≫

Clear cell variant of mucoepidermoid carcinoma arising in the submandibular gland

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Abstract : We present the second case of mucoepidermoid carcinoma, clear cell variant, originating from the submandibular gland. The tumor of 75-year-old Japanese man histologically consisted of predominantly clear cells, epidermoid cells, a small amount of mucous cells and intermediate cells. Glycogen particles were detected in the cytoplasm. Immunohistochemically, tumor cells were diffusely positive for p63. Finally, we would like to put emphasis on the importance of detection of epidermoid cells on extensive histochemical study of PAS and Alcian blue stains and immunohistochemistry of p63, particularly in the distinction from acinic cell carcinoma or clear cell carcinoma, NOS.

Keywords : mucoepidermoid carcinoma, clear cell variant, submandibular gland.

INTRODUCTION

Clear cell neoplasm arising in the salivary gland may pose a diagnostic challenge and several lesions including mucoepidermoid carcinoma, acinic cell carcinoma, clear cell oncocytoma, epithelial-myoepithelial carcinoma, clear cell adenocarcinoma and metastatic renal cell carcinoma should be distinguished. In most cases of mucoepidermoid carcinoma, the clear cell components comprise of approximately 10% of the total tumor volume and rarely show the dominant clear cell cytoplasm.[1] In this article, we report the second case of mucoepidermoid carcinoma, clear cell variant, arising from the submandibular gland.

CASE REPORT

A 75-year-old Japanese man presented with swelling of left submandibular area and the magnetic resonance imaging disclosed the tumor of the left submandibular gland. Systemic imaging analyses revealed no distant metastatic lesions including kidney. On the diagnosis of salivary gland tumor, the resection of the left submandibular gland was performed.

The surgically resected specimen was routinely processed for histological examination. Briefly, the specimen was fixed with 10% formalin and embedded in paraffin wax. Four-micron tissue sections were stained with hematoxylin-eosin, periodic acid-Schiff (PAS) with and without diastase treatment, Alcian blue and immunohistochemical stains. Primary antibodies against cytokeratin 5 (XM26, 1:800, Novocastra Laboratories Ltd, Newcastle, UK), cytokeratin 7 (OV-TL 12/30, 1:800, DAKO, Glostrup, Denmark), p63 (4A4, 1:800, LAB VISION, CA, USA), α 1-antitrypsin (polyclonal, 1:1600, DAKO, Glostrup, Denmark), α 1-antichymotrypsin (polyclonal, 1:2000, DAKO, Glostrup, Denmark), CD56 (123C3, 1:200, ZYMED Laboratories, CA, USA), S-100 protein (polyclonal, 1:2400, DAKO, Glostrup, Denmark), chromogranin A (polyclonal, prediluted, DAKO, CA, USA), synaptophysin (polyclonal, prediluted, DAKO, CA, USA), alpha smooth muscle actin (1A4, 1:800, DAKO, Glostrup, Denmark) and GFAP (polyclonal, 1:3200, DAKO, Glostrup, Denmark) were employed in the present study.

Post-radiation therapy, total 50Gy, was

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performed because of the positivity of surgical margin. The postoperative course was uneventful without local recurrence or metastasis four months after the operation.

PATHOLOGICAL FINDINGS

Macroscopic findings

The tumor measuring 25x20x17mm was observed in the left submandibular gland. The cut surface of the tumor showed whitish color with ill-defined margin (Figure 1).

Microscopic findings

The tumor had ill-demarcated margin in the interface to normal submandibular gland (Figure 2A). The tumor consisted of predominant clear cells and focal epidermoid eosinophilic cells with intercellular bridging (Figure 2B, C), but there were no evident glandular structures or myoepithelial cells. Small cells with eosinophilic cytoplasm and without intercellular bridging, suggesting intermediate cells, were also identified (Figure 2D). Intracytoplasmic vacuoles were scattered. There was no anaplasia in the tumor cells. Mitotic figures were less than 4 per 10 high power fields. Cystic formation accounted for less than 20% of the total tumor volume. Neural invasion was focally identified (Figure 2E). Although hemorrhage was focally seen, necrosis was absent. Hyalinization was observed in the stroma.

Histochemical findings

PAS stain with and without diastase treatment detected glycogen in the cytoplasm of tumor cells and focal mucin deposition into the tumor nests (Figure 3A) Additionally, Alcian blue stain also highlighted the focal mucous materials (Figure 3B)

Immunohistochemical findings

Neoplastic cells were diffusely positive for cytokeratin 5, cytokeratin 7, p63 and Keratin 903 and focally positive for α1-antitrypsin, α1-antichymotrypsin and CD56. Clear cells were positive for cytokeratin 5, cytokeratin 7, p63

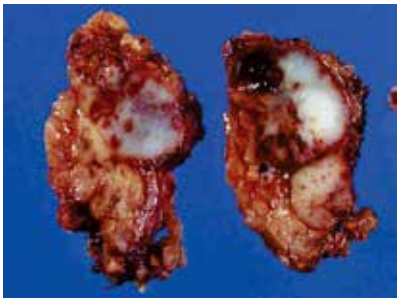

Fig. 1

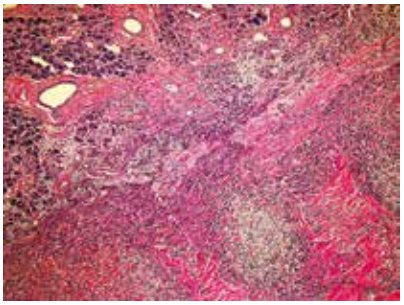

Fig. 2A

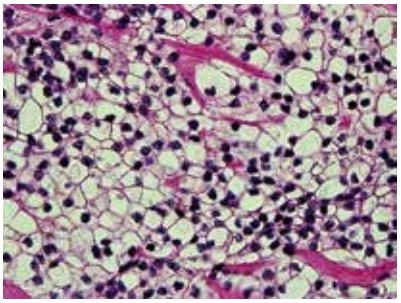

Fig. 2B

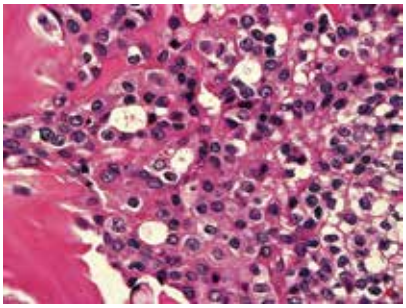

Fig. 2C

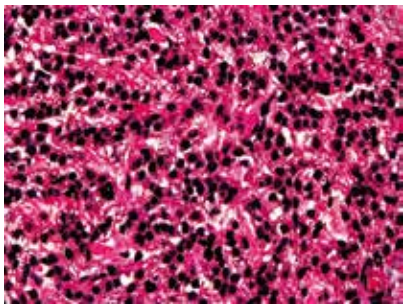

Fig. 2D

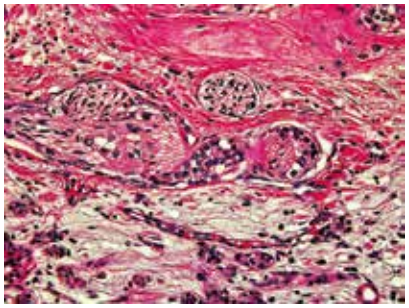

Fig. 2E

FIG.1: Macroscopic findings. The whitish tumor with ill-defined margin is observed in the left submandibular gland.

FIG.2: Microscopic findings. (A) At the interface between the tumor and submandibular gland, the infiltrating margin is observed. (B) Neoplastic cells with clear cytoplasm possess slightly enlarged nuclei with irregular margin. (C) Epidermoid cells with eosinophilic cytoplasm and intercellular bridging are seen. (D) The proliferation of small cells with eosinophilic cytoplasm suggesting intermediate cells is noted. (E) The perineural invasion is shown.

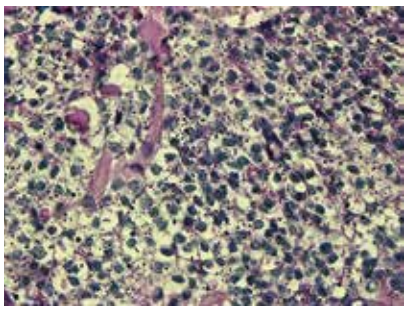

Fig. 3A

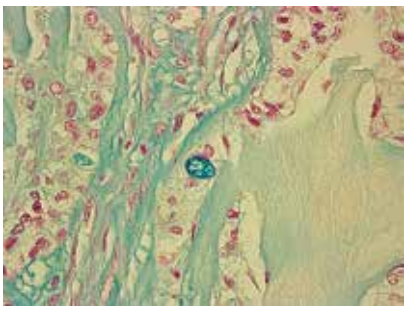

Fig. 3B

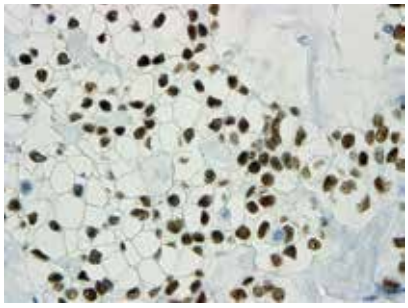

Fig. 4

FIG.3: Histochemical findings (A) periodic acid-Schiff stain. Glycogen particles are observed in the cytoplasm. (B) Alcian blue stain. Focal mucin deposition is seen into the tumor nests.

FIG.4: Immunohistochemical finding. Neoplastic cells with clear cytoplasm show diffuse positivity for p63.

(Figure 4) and Keratin 903, whereas eosinophilic cells suggesting epidermoid or intermediate cells were positive for cytokeratin 5, p63 and Keratin 903. However, S-100 protein, synaptophysin, chromogranin A, alpha smooth muscle actin and GFAP were completely negative.

Final diagnosis

We diagnosed this tumor as mucoepidermoid carcinoma, clear cell variant. According to the present WHO classification, low grade malignant was considered on the basis of less than 20% of intracystic space, the presence of neural invasion, absence of necrosis, absence of anaplasia and less than 4 of mitotic figures per 10 high power fields.

DISCUSSION

Pathologists should distinguish mucoepidermoid carcinoma from acinic cell carcinoma, clear cell oncocytoma, epithelial-myoepithelial cell carcinoma, myoepithelial carcinoma, clear cell carcinoma, NOS, and metastatic renal cell carcinoma.[1-6] In acinic cell carcinoma, PAS stain with diastase treatment can detect zymogen granules. However, there were no zymogen granules in this case. In the distinction from clear cell oncocytoma, we did not detect the proliferating area of oncocytes. Additionally, no evident differentiation into myoepithelial cells was observed on routine HE stain and immunohistochemical stain for alpha smooth muscle actin and S-100 protein. Clear cell carcinoma, NOS, predominantly affects minor salivary gland, possesses no mucin in the tumorous area and lacks epidermoid cells showing positivity for p63. Finally, this patient had no renal tumors using systemic imaging analyses. Accordingly, we diagnosed this tumor as mucoepidermoid carcinoma, clear cell variant, low grade. Herein, we again would like to put emphasis on the importance of recognition of epidermoid cells on routine HE stain and the identification of a small amount of mucous cells using extensive histochemical study, particularly in the distinction from acinic cell carcinoma.[3,5]

Histologically, mucoepidermoid carcinoma consists of epidermoid cell, intermediate cell (undifferentiated small cell) and mucus cell. This tumor is usually called as typical variant. However, some tumors may contain columnar, clear cell and eosinophilic/oncocytoid cells.[1-6] On average, clear cell component accounts for about 10% of the cell population of mucoepidermoid carcinoma.[1] However, some tumors comprise a large portion of the tumor and such a tumor is designated as clear cell variant.[2-7] Clear cell variant of mucoepidermoid carcinoma occurs in nasal cavity, larynx, skin, conjunctiva, bone and respiratory tract as well as salivary gland.[8-13] Regarding clear cell variant of mucoepidermoid carcinoma, there is only one tumor arising in submandibular gland.[14] As for variant of mucoepidermoid carcinoma, squamoid and eosinophilic variants have been reported in addition to clear cell variant.[14] Clear cell variant accounts for 7.5% of mucoepidermoid carcinoma.[14] Epidermoid cells or intermediate cells have been suggested as the origin of clear cells using routine histological, immunohistochemical, and ultrastructural methods.[1,3,5,8,15] In the present study, clear cells as well as eosinophilic cells including

epidermoid and intermediate cells showed the positivity for p63. Therefore, we suggest that clear cells in mucoepidermoid carcinoma may derived from epidermoid and intermediate cells. In our experience, the detection of intermediate cells in rare variants of mucoepidermoid carcinoma seems to be more difficult than typical variant. The clear cytoplasm in salivary gland neoplasm is due to the abundant glycogen, scarce organelles, amorphous material or fixation artifact.[1-4,8] All three tumors genetically examined in clear cell variant of mucoepidermoid carcinoma, t(11;19) translocation has been identified.[14] The quantity of clear cell in mucoepidermoid carcinoma does not give an impact the grade or prognosis.[1,16] However, a large scale study will be needed in order to elucidate the clinical and pathological characteristics of clear cell variant of mucoepidermoid carcinoma.

In conclusion, we present the second case of mucuepidermoid carcinoma, clear cell variant, arising from the submandibular gland. Pathologists should recognize the presence of this tumor in the differential diagnosis of salivary gland neoplasms with clear cell cytoplasm.

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