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Case Report

Cystadenocarcinoma of the minor salivary gland arising in the upper lip: A surgical case of an inadequate cytology specimen hampering conclusive diagnosis

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ABSTRACT

Cystadenocarcinoma (CAC) of the salivary gland poses a diagnostic challenge to us, as this uncommon entity is extremely difficult to diagnose pre-operatively on an inadequate sample. However, markedly few papers have described the cytological features of CAC. An 82-year-old male presented with a history of a gradual increase in size and occasional mucous drainage from a swollen reddish nodule on the right upper lip. A retrospective examination of the cytological specimens from the drainage revealed a small number of clusters and scattered single cells of severely degenerated and mildly atypical epithelial cells with hyperchromatic dense nuclei and abundant clear cytoplasm, in a background of a large amount of mucinous material. We first interpreted this finding merely as the presence of atypical cells. However, a gross examination revealed a non-capsulated and relatively well-demarcated cystic lesion, grayish to whitish in color and measuring 13 × 9 mm in diameter, filled with mucin. A microscopic examination showed that the tumor had a central cystic cavity filled with mucinous material and was predominantly composed of the papillary proliferation of atypical columnar mucous epithelial cells with enlarged hyperchromatic nuclei, mixed with mitotic hot spots often projecting and melting into the mucinous cystic lumen, and focally involving the surrounding connective tissue. Therefore, we ultimately made a diagnosis of CAC of the minor salivary gland arising in the upper lip. Given the characteristic features of CAC, cytopathologists should be able to correctly diagnose this lesion based on multiple adequate fine needle aspiration samples.

1. Introduction

Among epithelial salivary gland neoplasms, cystadenocarcinoma (CAC) is uncommon and only accounts for approximately 0.18% of cases [1]; however, it constitutes up to nearly 2% of all malignant salivary gland tumors [2,3]. CACs are known to occur most commonly in the major salivary glands and tend to involve the parotid glands of patients over 50 years old [3,4]. Our thorough investigation revealed that, to date, less than 100 cases of true salivary gland CAC have been reported in the English literature.

CAC of the salivary gland is defined conceptually as the malignant counterpart of non-Warthin benign cystadenoma [3–5] and frequently poses a diagnostic challenge to clinicians and cytopathologists, as this rare entity is extremely difficult to diagnose pre-operatively from an inadequate or small sample. Indeed, even the WHO classification of salivary gland tumors in 2005 described CAC merely as a rare malignant tumor characterized predominantly by a cystic pattern, often displaying an intraluminal papillary growth pattern [5]. Furthermore, CACs can be slow-growing and asymptomatic tumors, as most are not widely invasive on the gross and histological findings and often have a similar clinical presentation to cystadenomas. However, recurrence and metastasis to the regional lymph nodes have been reported in patients with high-grade, poorly differentiated CAC [3–5].

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Further hampering accurate diagnosis, even the cytomorphology observed using fine needle aspiration (FNA) specimens might result in a misdiagnosis as cystic mucoepidermoid carcinoma or papillary-cystic variant of acinic cell carcinoma, and Warthin's tumor, non-Warthin cystadenoma, or salivary gland cysts (ranging from malignant to benign), the latter benign lesions of which are much more indolent than CAC [6,7]. The early accurate diagnosis and conservative but complete resection of CACs might allow for an improved quality of life and an increase in the survival rates of these patients. However, few reports have described the cytological features of CAC on FNA.

We herein report an extremely rare case of CAC originating from the minor salivary gland of the right upper lip. The inadequacy of the cytology specimen hampered conclusive diagnosis, and the diagnosis was ultimately made based only on the mucous drainage, not the findings of FNA.

2. Report of case

An 82-year-old male presented with a gradual increase in the swelling of a reddish nodule on the right upper lip, measuring approximately 20 × 20 mm in diameter, covered by smooth oral mucosa and accompanied by a central ulcerated fistula with occasional mucous drainage (Fig. 1A). He had an unremarkable medical history, except for essential hypertension. The laboratory data, including the blood cell count, chemistry, and tumor markers, were within normal limits, except for a modestly elevated level of cytokeratin 19 fragment (CYFRA; 3.6 ng/mL). Oral ultrasonography revealed a heterogeneous but enhanced and well-demarcated nodule, measuring approximately 20 × 10 × 5 mm in diameter, accompanied by several low-echoic trabecular-like structures (Fig. 1B). The encysted fluid content generated a moderately high (white) signal intensity on T2-weighted magnetic resonance imaging (MRI) (Fig. 1C). Full-body computed tomography (CT) scans and positron emission tomography with 2-deoxy-2-[^{18}F] fluoro-D-glucose (^{18}F-FDG PET) revealed no definite evidence of metastases in the lymph nodes or other organs. Based on these findings, the clinicians first interpreted this lesion as a benign tumor or cyst, such as a mucous retention cyst, but could not completely rule out malignancy.

The small and inadequate specimen from the pre-operative mucous drainage retrospectively contained a small number of clusters and scattered single cells, which were severely degenerated and mildly atypical epithelial cells with hyperchromatic dense nuclei and abundant clear cytoplasm, in a background of a large amount of mucinous and proteinaceous material, with Papanicolaou staining (Fig. 2A). These clusters of tumor cells sometimes exhibited mildly three-dimensional structures (Fig. 2B). There was no evidence of necrotic or hemorrhagic background; however, many tiny clusters of markedly degenerated cells were recognized (Fig. 2A). FNA cytology had never been performed. Although one additional Giemsa staining was performed, no further information was gained. We first diagnosed this finding merely as the presence of atypical cells, given its cytologically severe degenerative features in a small volume.

Tumor extirpation was performed, and a gross examination of the cut surface displayed a non-capsulated, relatively firm and well-demarcated cystic lesion grayish to whitish in color and measuring 13 × 9 mm in diameter, centrally filled with mucin (Fig. 3A). On scanning magnification, the tumor was found to contain a central cystic cavity filled with mucinous material and showed an uncapsulated and partly poorly-circumscribed cystic nodule, focally involving the surrounding connective tissue of the minor salivary gland (Fig. 3B). Resection was diagnosed as complete by this histopathological examination.

Microscopically, the tumor predominantly comprised a proliferation of atypical columnar epithelial cells, largely arranged in a papillary (Fig. 4A) growth pattern with delicate fibrovascular cores, partially invading

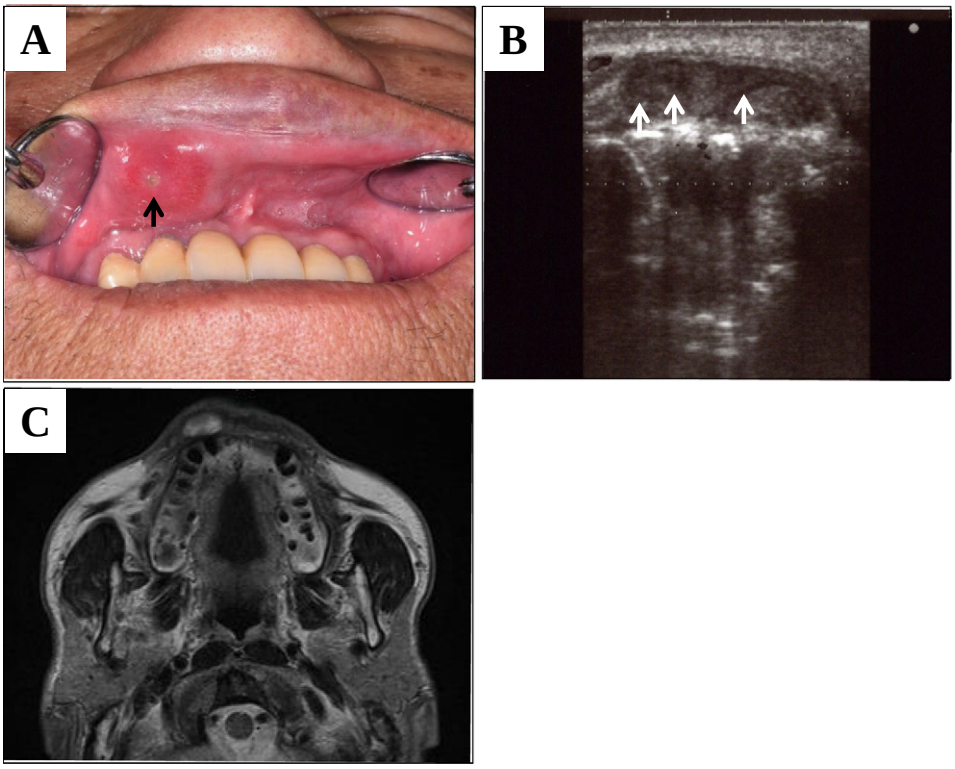

Fig. 1. The clinical findings, including ultrasonography and MRI at surgery, of the CAC specimens. (A) The patient complained of a gradual increase in the swelling of a reddish nodule on the right upper lip, measuring approximately 20 × 20 mm in diameter, covered by smooth oral mucosa and accompanied by a central ulcerated fistula (arrow) with occasional mucous drainage. (B) Oral ultrasonography revealed a heterogeneous but enhanced and well-demarcated nodule, measuring approximately 20 × 10 × 5 mm in diameter, accompanied by several low-echoic trabecular-like structures (arrows). (C) The encysted fluid content generated a moderately high signal intensity on T2-weighted MRI.