
점액세포가 관찰되는 침샘 관암종
-세침흡인 세포검사에서 점액표피모양암종으로 오인했던 1예 보고-

연세대학교 의과대학 병리학교실, 연세대학교 치과대학 구강병리학교실,¹
영동세브란스병원 진단병리과²

김혜령·김현기·김호근·김진¹·홍순원²·김세훈

= Abstract =

Salivary Duct Carcinoma with Mucin Containing Cells
-Report of a Case Misdiagnosed as Mucoepidermoid Carcinoma on
Fine Needle Aspiration Cytology-

Haeryoung Kim, M.D., Hyunki Kim, M.D., Hoguen Kim, M.D., Jin Kim, D.D.S.,¹
Soon Won Hong, M.D.,² and Se Hoon Kim, M.D.

Department of Pathology, Yonsei University College of Medicine,

¹Department of Oral Pathology, Yonsei University College of Dentistry, and

²Department of Pathology, Yongdong Severance Hospital, Seoul, Korea

Salivary duct carcinoma (SDC) is a rare primary salivary gland malignancy characterized by histological features similar to those of ductal carcinomas of the breast. It is regarded as a high-grade malignancy associated with frequent local recurrences and early distant metastases that require aggressive treatment. The typical fine needle aspiration cytology (FNAC) findings in SDC include cellular smears showing tumor cells with eccentric pleomorphic nuclei and a granular cytoplasm arranged in flat sheets or cribriform patterns against a necrotic background. However, the presence of mucin-containing cells in SDC has been rarely described. We report the FNAC findings in a patient with histologically confirmed SDC that demonstrated numerous mucin-containing cells and was subsequently misdiagnosed as a high-grade mucoepidermoid carcinoma. Here we discuss the problems involved in distinguishing SDC from high-grade mucoepidermoid carcinoma on the basis of cytologic findings alone.

Key words: Salivary duct carcinoma, Mucin, Fine needle aspiration cytology

논문접수 : 2006년 1월 13일
게재승인 : 2006년 2월 23일

책임저자 : 김 세 훈

주 소 : (120-752) 서울특별시 서대문구 신촌동 134, 연세대학교 의과대학 병리학교실

전 화 : 02-2228-1769

팩 스 : 02-362-0860

E-mail address : paxco@yumc.yonsei.ac.kr

INTRODUCTION

Salivary duct carcinoma (SDC) is a rare type of malignancy of salivary gland origin and accounts for 9% of all salivary gland malignancies.¹ It is characterized by histological features that are strikingly similar to those of ductal carcinomas of the breast, including solid, papillary, and cribriform patterns, and comedo-type necrosis. It has a marked tendency to invade the facial nerve and permeate lymph vessels, resulting in frequent local recurrences and early distant metastases. It is regarded as a high-grade malignancy.²⁻⁶ Aggressive treatment including radical surgery and postoperative radiotherapy is recommended for patients with SDC. An accurate preoperative diagnosis by fine needle aspiration cytology (FNAC) may be valuable for planning the extent of treatment in advance.

A few reports on FNAC findings in SDC appear in the literature, vast proportion of them were initially misdiagnosed as high-grade mucoepidermoid carcinoma. The typical picture in FNAC specimens obtained from patients with SDC consists of tumor cells with eccentric pleomorphic nuclei and granular cytoplasm arranged in flat sheets with cribriform patterns against a necrotic background.⁷⁻¹⁹ However, the presence of mucin-containing cells in SDC has been rarely described in the literature.^{2,3,8,10,13,20,21} This finding may help exclude a diagnosis of SDC.^{9,14,16,17}

We report a case of SDC that we recently encountered. We failed to recognize this disorder initially using FNAC findings alone because of several mucin-containing cells within the aspirated material. This finding lead to an erroneous diagnosis of a high-grade mucoepidermoid carcinoma.

CASE

A 62-year-old man presented with a palpable mass in his left preauricular area, reporting symptoms for the last 3 months. The mass was firm and slightly tender on palpation and measured about 3.5 cm in diameter. He did not have a history of medical or surgical illnesses.

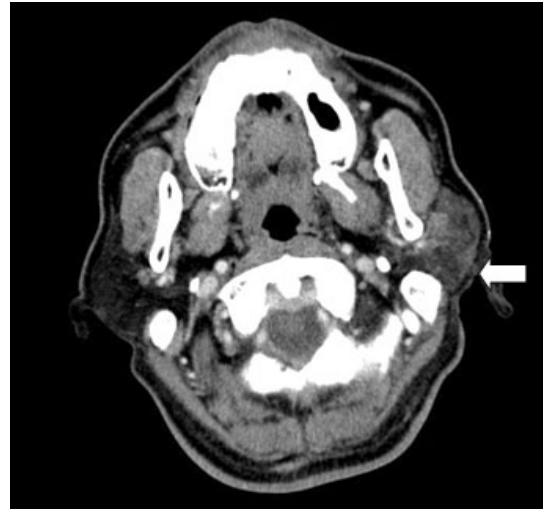


Fig. 1. Computed tomography of the neck. An ill defined mass with mixed enhancement is present in the superficial lobe of the left parotid gland (white arrow).

Laboratory results were all within normal limits. Ultrasonography and computed tomography revealed an ill-defined, lobulated, 3.4 cm mass with mixed echogenicity and enhancement, respectively, in the superficial lobe of the left parotid gland (Fig. 1). There was no evidence of extraglandular extension or enlarged cervical lymph nodes. A biopsy of the mass was removed by FNAC guided by ultrasound, and a diagnosis of "positive for malignancy - most likely a high-grade mucoepidermoid carcinoma" was given based on the cytologic findings. A total parotidectomy was performed 3 weeks after the diagnosis. The operative finding was a mass located across the superficial and deep lobes with attachment to the facial nerve. The patient is currently receiving postoperative radiotherapy.

Cytologic Findings

The smears obtained by FNAC were stained using the Papanicolaou method and demonstrated a highly cellular smear consisting mostly of irregular clusters in a dirty background at scanning power. The cellular groups were arranged in flat sheets or in papillary configurations, and distinct cribriform patterns were noted in some areas (Fig. 2A). The cytological features of individual tumor cells were variable. The majority of them showed a highly

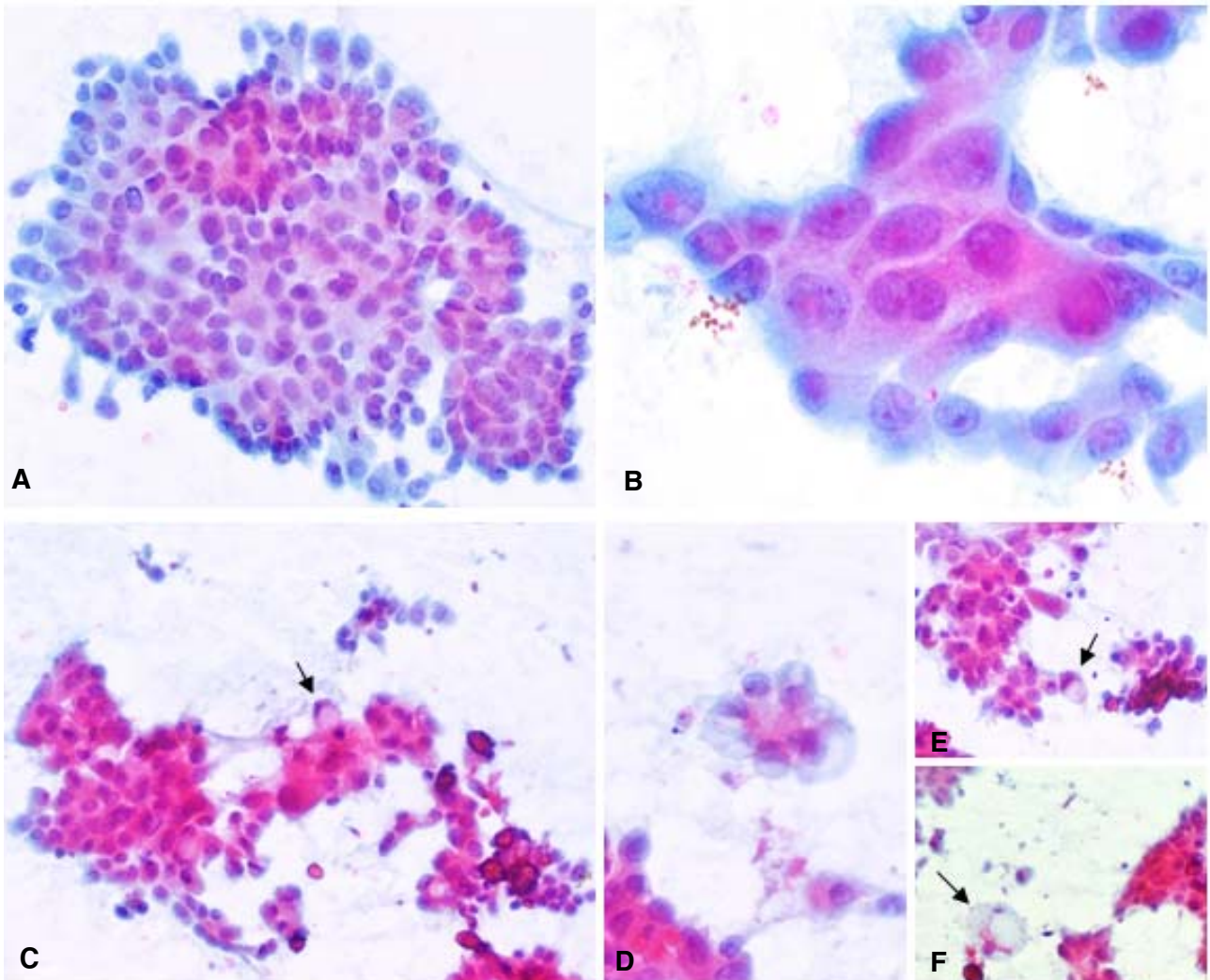


Fig. 2. Cytologic findings. **(A)** A distinct cribriform pattern is seen in the cluster of tumor cells. The individual cells show eccentrically placed, relatively monomorphic nuclei with an ample amount of granular cytoplasm. **(B)** Higher power view demonstrates larger cells with pleomorphic nuclei, prominent nucleoli, and abundant eosinophilic granular cytoplasm. **(C-F)** Numerous tumor cells containing vacuolated cytoplasm are seen among the clusters, some resembling signet ring cells (arrows). (Papanicolaou)

granular cytoplasm, and the nuclei were located eccentrically, the latter feature being more easily appreciated within the cribriform clusters. The nuclei were relatively monomorphic, especially in the tighter clusters, with fine chromatin and small conspicuous nucleoli. Mitotic figures were rarely seen. A second population of tumor cells was characterized by an abundantly granular and sometimes finely vacuolated cytoplasm with indistinct borders (Fig. 2B). The cells were either ovoid or squamoid in shape, and the squamoid cells failed to reveal any definite intercellular

bridges or evidence of keratinization, which is characteristic of tumor cells of squamous-cell origin. The nuclei of these cells were relatively pleomorphic, with relatively coarse chromatin and large, conspicuous nucleoli. There was another distinct population of cells: the constituent cells that were individually scattered among the clusters or sheets and contained large cytoplasmic vacuoles that seemed to push the nuclei to one border, simulating the appearance of a typical signet ring cell (Fig. 2C-F).



Fig. 3. Gross finding. The left parotid gland shows a 1.5x1.5cm sized pinkish gray ill defined, multiloculated cystic mass, filled with grayish mucoid material (lower left).

Gross Findings

On gross examination, the left parotid gland measured 5.0 × 3.8 × 3.0 cm overall and contained a previously collapsed pinkish-gray multiloculated cystic mass measuring 1.5 × 1.5 cm, that was extruding a grayish

mucoid material (Fig. 3). The mass had an ill-defined but vaguely lobulated appearance. No hemorrhage was present. The remaining parotid gland parenchyme was unremarkable.

Histologic Findings

Microscopic examination of the tumor revealed an infiltrative mass composed predominantly of well-defined islands of epithelial cells arranged in an intraductal cribriform or micropapillary pattern with lumina and central comedo-type necrosis, remarkably similar to the findings in typical mammary ductal carcinoma in situ (Fig. 4A, B). The lumina of some epithelial islands contained wispy bluish-gray material. Smaller infiltrative groups of epithelial cells were associated with desmoplasia (Fig. 4C). The individual tumor cells had a relatively abundantly granular and eosinophilic cytoplasm, sometimes with apical snouts reminiscent of apocrine differentiation (Fig. 4D). The nuclei were round to oval in shape and eccentrically located, and contained

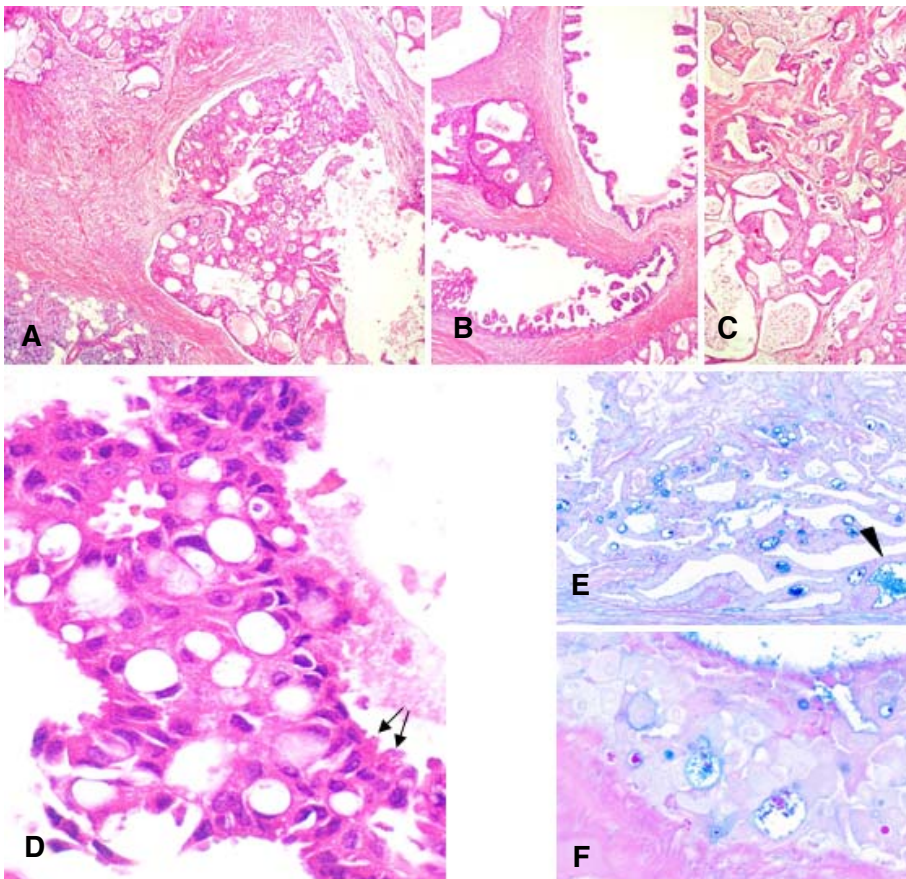


Fig. 4. Histologic findings. (A, B) Epithelial cell islands with cribriform (A) and micropapillary (B) patterns resembling mammary ductal carcinomas are seen at low power magnification. (C) Infiltrative areas are associated with desmoplastic stroma. (D–F) High power view reveals mucin containing cells within the cribriform clusters as well as tumor cells with eosinophilic cytoplasm and apical snouts (arrow). The lumens in the cribriform clusters contain mucin (arrowhead). (E, alcian blue; F, Periodic acid schiff)

prominent nucleoli. They also showed marked pleomorphism in most areas. Tumor cells in the cribriform areas had a relatively smaller amount of eosinophilic, granular cytoplasm, and their nuclei were less pleomorphic. Mucin-containing vacuolated cells were intermingled with the other tumor cells and showed a cytoplasm that was distended with large vacuoles compressing the nuclei (Fig. 4D). Alcian blue and periodic acid-Schiff stains confirmed that these latter cells and the bluish-gray intraluminal material contained mucin (Fig. 4E, F). There was no evidence of perineural or lymphovascular invasion.

DISCUSSION

The FNAC findings in SDC have rarely been discussed in the literature. Although retrospective examination of the FNAC samples of most reported cases have shown characteristic features that theoretically may be of help in its diagnosis,⁷⁻¹⁹ in practice it is not easy to make a definitive diagnosis of SDC purely on the basis of the cytological findings alone. Most fine needle aspirates obtained from individuals with SDC, as described in the literature, have demonstrated the following features in common: a cellular smear showing cribriform clusters or flat sheets of cells, tumor cells with abundant granular cytoplasm and eccentrically located nuclei with coarse chromatin and prominent nucleoli, and a background of necrosis. Additional features such as intranuclear inclusions resembling those observed in papillary thyroid carcinomas, cytoplasmic vacuoles, and foam cells have been reported,⁷ but these features were also disputed by others who argued that these findings were representative of degenerative change.^{9,13}

The main differential diagnosis on encountering such FNAC materials includes high-grade mucoepidermoid carcinomas, adenoid cystic carcinomas, acinic cell carcinomas, and oncocytic neoplasms. Of these, the high-grade mucoepidermoid carcinoma is probably the most difficult to be ruled out based on the cytological findings only. Most cases reported as SDC in the literature had originally been misdiagnosed as muco-

epidermoid carcinomas by FNAC. High-grade mucoepidermoid carcinomas are characterized by a distinctive three-cell population consisting of large epidermoid cells with abundant eosinophilic cytoplasm, intermediate cells which are smaller cells resembling endocervical or bronchial reserve cells with more uniform, darker nuclei and scant cytoplasm, and a final population of mucin-producing cells with abundant vacuolated cytoplasm.²² Extracellular mucin is also evident in the background. Cellular smears showing a co-existence of three different populations of tumor cells along with the mucinous background have been regarded as important criteria in the diagnosis of mucoepidermoid carcinomas and in the exclusion of SDC. However, as in the present case, evidence of mucin has sometimes been observed in otherwise typical SDC,^{2-5,8} subsequently bringing up more confusion in the differential diagnosis.

The mucin content in SDC has varied in extent and location in different reports. Most cases of SDC have shown only focal luminal or interstitial deposition of mucin,^{4-6,12} although occasionally tumor cells with intracellular mucin have also been demonstrated.^{2,3,8,10,13,20} At the other extreme lie four cases of mucin-rich variants of SDC reported by Simpson et al.,²³ which are characterized by clusters of epithelial cells otherwise resembling those constituting typical SDC, but floating in pools of mucin. Interestingly, an immunohistochemical study performed by the authors revealed that all cases showed MUC2 expression both in the tumor cell cytoplasm and in the extracellular mucin lakes. There was also cytoplasmic expression of gastric type mucin, MUC6, and MUC5B, a mucin type normally found in mucus-secreting cells of salivary glands. The mucin content in our case was not extensive enough to qualify as a mucin-rich variant. Nevertheless the present case is of great significance in that numerous scattered tumor cells containing intracytoplasmic mucin were present in the FNAC smear, leading to an erroneous diagnosis of mucoepidermoid carcinoma.

As mucin may be observed both intracellularly and extracellularly and even forms lakes as described in mucin-rich variants, the presence or absence of mucin should not be regarded as an important factor in the

differential diagnosis between mucoepidermoid carcinomas and SDC. Instead, the presence of an epidermoid cell component with intercellular bridges and evidence of keratinization, and intermediate cells would be more reliable findings in distinguishing between the two malignancies. The presence of cribriform structures, along with the abundant granular or finely vacuolated cytoplasm and eccentrically located nuclei of tumor cells would be helpful in favoring a diagnosis of SDC.^{8,11} Another possible cause of confusion between these two entities may be the scattered necrotic cells with dense eosinophilic cytoplasm which actually correspond to the comedo-type necrosis of SDC on the tissue sections but may be mistaken for the squamous cell component of mucoepidermoid carcinoma, especially in the presence of scattered mucin-containing cells.

In summary, FNAC of SDC can demonstrate a great variety of cytologic features, including presence of mucin-containing cells, which may cause difficulty in differentiating this entity from high-grade mucoepidermoid carcinoma. Presence of cribriform groups of tumor cells with eccentrically located nuclei and granular cytoplasm and the absence of a distinctive three-cell population characteristic of mucoepidermoid carcinomas would support the diagnosis of SDC, based on the cytologic findings. However, in practice it will not be possible to distinguish between the two entities with confidence, especially in situations when numerous mucin-containing cells are noted.

REFERENCES

1. Barnes L, Everson JW, Reichart P, Sidransky D. WHO Classification of Tumours. Pathology and Genetics. Head and Neck Tumours. Lyon: IARC-Press, 2005;236-7.
2. Hui KK, Batsakis JG, Luna MA, Mackay B, Byers R. Salivary duct adenocarcinoma: a high grade malignancy. *J Laryngol Otol* 1986;100:105-14.
3. Simpson RHW, Clarke TJ, Sarsfield PTL, Babajews AV. Salivary duct carcinoma. *Histopathology* 1991;18:229-35.
4. Kumar RV, Kini L, Bhargava AK, et al. Salivary duct carcinoma. *J Surg Oncol* 1993;54:193-8.
5. Delgado R, Vuitch F, Albores Saavedra J. Salivary duct carcinoma. *Cancer* 1993;72:1503-12.
6. Murrah VA, Batsakis JG. Salivary duct carcinoma. *Ann Otol Rhinol Laryngol* 1994;103:244-7.
7. Gal R, Strauss M, Zohar Y, Kessler E. Salivary duct carcinoma of the parotid gland. Cytologic and histopathologic study. *Acta Cytol* 1985;29:454-6.
8. Dee S, Masood S, Issacs JH, Hardy NM. Cytomorphologic features of salivary duct carcinoma on fine needle aspiration biopsy. A case report. *Acta Cytol* 1993;37:539-42.
9. Elsheikh TM, Bernacki EG, Pisharodi L. Fine needle aspiration cytology of salivary duct carcinoma. *Diagn Cytopathol* 1994;11:47-51.
10. Colecchia M, Frigo B, Leopardi OM. Salivary duct carcinoma of the parotid gland. Report of a case with cytologic and immunocytochemical findings on fine needle aspiration biopsy. *Acta Cytol* 1997;41:593-7.
11. Fyrat P, Cramer H, Feczko JD, et al. Fine needle aspiration biopsy of salivary duct carcinoma: report of five cases. *Diagn Cytopathol* 1997;16:526-30.
12. Park A, Kim HJ, Kim DW, Lee DW. Fine needle aspiration cytology of salivary duct carcinoma - a case report. *Korean J Cytopathol* 1997;8:143-9.
13. Khurana KK, Pitman MB, Powers CN, Korourian S, Bardales RH, Stanley MW. Diagnostic pitfalls of aspiration cytology of salivary duct carcinoma. *Cancer (Cancer Cytopathol)* 1997;81:373-8.
14. Klijanienko J, Vielh P. Cytologic characteristics and histomorphologic correlations of 21 salivary duct carcinomas. *Diagn Cytopathol* 1998;19:333-7.
15. Chen KTK. Cytology of salivary duct carcinoma. *Diagn Cytopathol* 2000;22:132-4.
16. Garcia Bonafe M, Catala I, Tarragona J, Tallada N. Cytologic diagnosis of salivary duct carcinoma: a review of seven cases. *Diagn Cytopathol* 1998;19:120-3.
17. Domson KK, Wakely PE. Aspiration and imprint cytopathology of salivary duct carcinoma. *Cancer (Cancer Cytopathol)* 1997;81:281-6.
18. Gilcrease MZ, Guzman Paz M, Froberg K, Pambuccian S. Salivary duct carcinoma. Is a specific diagnosis possible by fine needle aspiration cytology? *Acta Cytol* 1998;42:1389-96.
19. Yun KJ, Han WC, Jo JH, Lee KM. Fine needle aspiration cytology of salivary duct carcinoma with calcification in submandibular gland - a case report. *Korean J Cytopathol* 2001;12:49-52.
20. Kapadia SB, Barnes L. Expression of androgen receptor, gross cystic disease fluid protein, and CD44 in salivary duct carcinoma. *Mod Pathol* 1998;11:1033-8.
21. Oh YL. Fine needle aspiration cytology of high grade neoplasm and spindle cell lesion of salivary gland. *Korean J Cytopathol* 2005;16:75-87.

22. Cohen MB, Fisher PE, Holly EA, Ljung B-M, Lowhagen T, Bottles K. Fine needle aspiration biopsy diagnosis of mucoepidermoid carcinoma. Statistical analysis. *Acta Cytol* 1990;34:43-9.

23. Simpson RHW, Prasad AR, Lewis JE, Skalova A, David L. Mucin rich variant of salivary duct carcinoma: a clinicopathologic and immunohistochemical study of four cases. *Am J Surg Pathol* 2003;27:1070-9.