CASE REPORT

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Fine Needle Aspiration Cytology of Secretory Carcinoma of the Parotid Gland in a Young Patient

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ABSTRACT Secretory carcinoma (SC) is a rare recently described entity that has characteristics similar to those of secretory breast carcinoma. We report a case of a 23 years old male with a swelling on the parotid gland. The ultrasonography guided fine needle aspiration cytology was performed on mass. Cytologically, the background of the aspirate is composed of inflammatory cells admixed with mucinous material. There were isolated cells as much as loosely cohesive clusters making papillary follicle-like glands with eosinophilic material in the lumen. Tumor cells were medium-sized round shape and eccentric nuclei with prominent nucleoli, remarkably vacuolated cytoplasm. The parotidectomy was performed and the pathology report revealed a SC. Histologically, the tumor is composed of microcystic, follicular, and micropapillary areas. The cytoplasm is usually vacuolated with also clear eosinophilic appearance. Immunohistochemically, tumor cells labeled with S100, MUC-4. At 5 years, the patient is disease-free and under regular follow-up.

Keywords: Secretory carcinoma; MUC-4; cytology; S100; salivary gland

Secretory carcinoma (SC) is a newly described malignancy of the salivary gland, which is very similar in many features to secretary carcinoma of the breast. It is more common in elderly patients.[1-3] SC can be seen in different parts like salivary glands, breast, and lung.[4] When it is originated from salivary glands, patients usually present with painless lump.[5] It is caused by a recently described translocation that results in the *ETV6-NTRK3* fusion gene. Fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR) reverse transcription-PCR (RT-PCR) technique is currently acknowledged as the "gold standard" for the diagnosis.[1,4] Although there is no specific immune marker for the diagnosis, some immune markers can be used to exclude the most common differential diagnosis of this entity.[2] Since a large number of cases have not yet been described in the literature, the prognosis of the malignancy cannot be clarified yet.[6]

With this case report, we aimed to share the cyto-histopathological and immunohistochemical properties of the newly defined malignancy. Cytological diagnosis can sometimes be challenging so is the other types of salivary gland neoplasms. As in our case, specific morphological features may have contributed to the literature in cases where molecular techniques cannot be used.

CASE REPORT

A 23-year-old male patient with no previous history of any diseases was admitted with complaints of swelling and pain on the left parotid gland. Physical examination revealed a firm mass on the left parotid

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gland. He declared that it took 3-4 weeks since the emergence of the lesion. Ultrasonography (USG) showed a 2x1.9x1.5 cm solid lesion located on the tail of the parotid gland, without any pathological lymph nodes. Subsequently, USG-guided fine needle aspiration cytology (FNAC) was performed using a 23-gauge needle. The aspirated material was spread over two slides one of them was stained with May Grunwald Giemsa stain; the other one was stained with Papanicolaou stain. The remaining, if any, was added to the cell block preparation liquid obtained with a mixture of 96% ethyl alcohol and 4% buffered formalin.

FNAC showed a highly cellular component with either single or clustered epithelioid neoplastic cells. Some inflammatory cells such as histiocytes were seen in a mucinous background (Figure 1A). The tumor cells were consisting of three-dimensional clusters with prominently papillary configuration (Figure 1B). The cytologic features of the single cells are mostly alike signet-ring cells. The cells were with eccentric nuclei, abundant foamy cytoplasm with vacuoles (Figure 1C). A few binucleate forms were also present (Figure 1D). The tumor cells on cell block material were showing follicular structures in addition to the papillary structures on the slides (Figure 1E). The final diagnosis on cytology was malignant cytology which is referred to malignant category: Category VI according to the Milan System for Reporting Salivary Gland Cytopathology. The patient subsequently underwent a total parotidectomy without lymph node dissection. Gross examination revealed a 2.1×1.5×1.5 cm tan-white, firm, *heterogeneous* solid mass with *cystic-hemorrhagic*

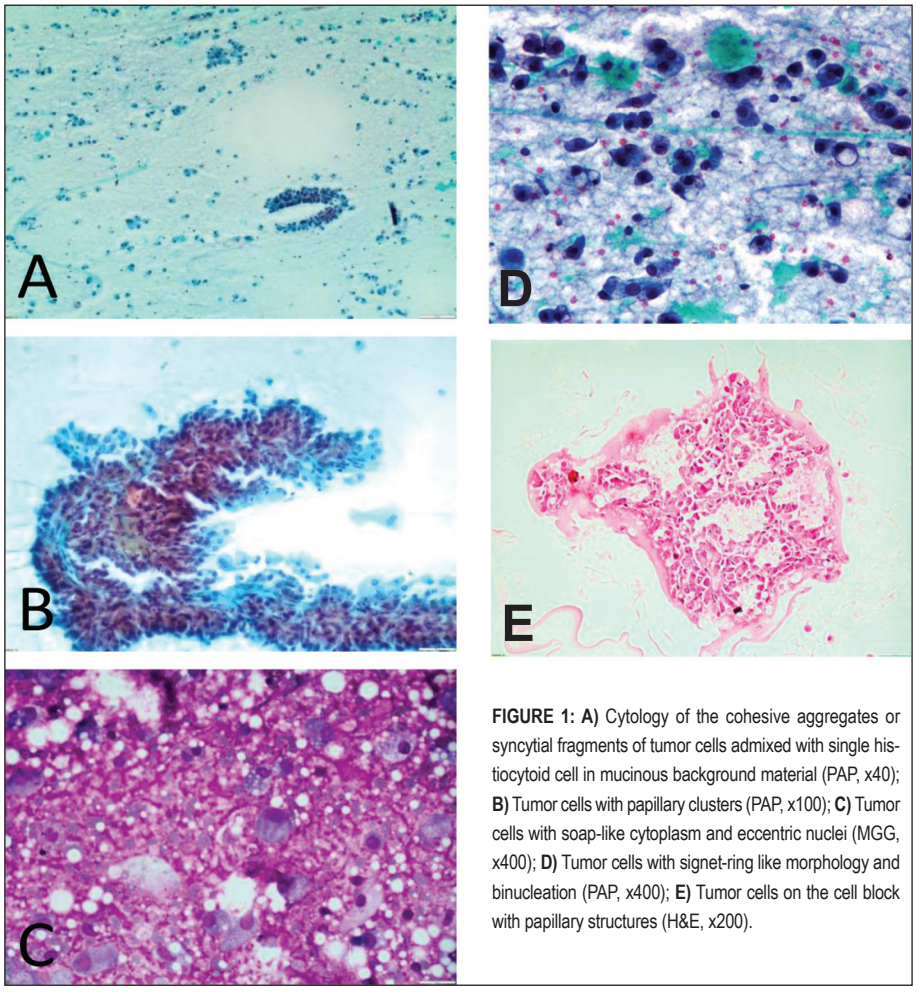

FIGURE 1: A) Cytology of the cohesive aggregates or syncytial fragments of tumor cells admixed with single histiocytoid cell in mucinous background material (PAP, x40); **B)** Tumor cells with papillary clusters (PAP, x100); **C)** Tumor cells with soap-like cytoplasm and eccentric nuclei (MGG, x400); **D)** Tumor cells with signet-ring like morphology and binucleation (PAP, x400); **E)** Tumor cells on the cell block with papillary structures (H&E, x200).

areas. Microscopically, the tumor was separated from the normal salivary gland with thick fibrous septa and showed mixed papillary, microcytic, and follicular growth patterns (Figure 2A, Figure 2B). The presence of abundant intraluminal eosinophilic *secretion was obtained.* Mitosis and necrosis were not observed.

Immunohistochemical staining was obtained on the parotidectomy specimen. The tumor cells showed diffuse positivity for cytokeratin 18, cytokeratin 19, GCDFP15, mammaglobin (Figure 2C) SOX-10 (Figure 2D), MUC-4 (Figure 2E), S100 (Figure 2F), pan-TRK, and negative staining for p63, DOG-1, thyroglobulin. The patient was subsequently diagnosed with SC of the parotid gland. He underwent radiation therapy. He is currently alive without recurrence at 5 years of follow-up. Written informed consent was obtained from the patient for that case report.

DISCUSSION

Secretory carcinoma is a salivary gland neoplasm firstly described as mammary analogue secretory carcinoma by Skalova and redesignated as a SC in the 2017 World Health Organization Classification of Head and Neck Tumors.[3]

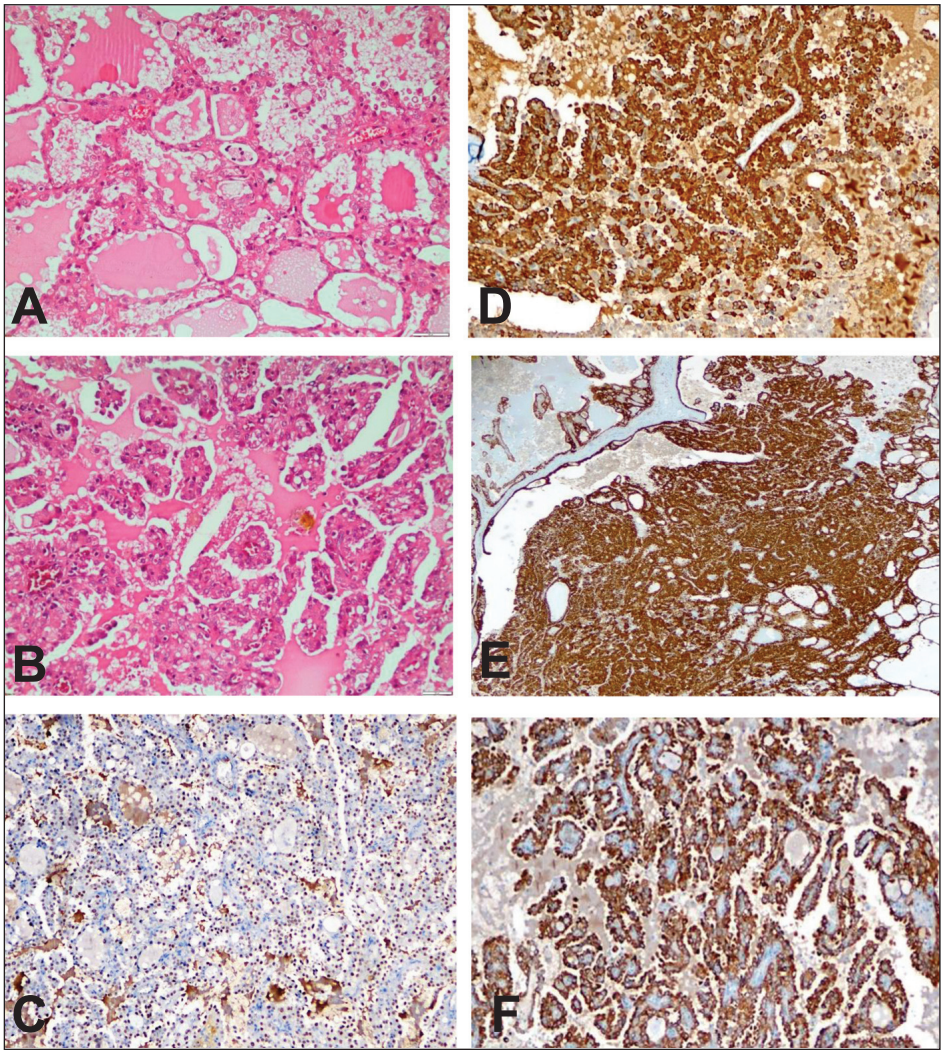

FIGURE 2: A) The tumor composed of follicular structures (H&E, x200); **B)** The tumor composed of papillary structures (H&E, x400); **C)** Mammoglobin expression (H&E, x100); **D)** SOX-10 expression (H&E, x100); **E)** MUC-4 expression (H&E, x100); **F)** S100 expression (H&E, x100).

SCs mostly affect adults without a sex predilection. Mostly, SC is located in the parotid gland and also it can be seen in other parts of the body such as the lung, thyroid gland, lip, sinonasal origin, and skin. Patients generally present with slowly growing painless lump. The prognosis of the SCs is still unknown due to the limited number of cases.[4,5,7]

Macroscopically, SC is described as well-circumscribed, unencapsulated tumors with solid and cystic areas.[7] In our study, tumor is well-circumscribed, unencapsulated as well.

Microscopically, on the cytology, SCs mostly described with mucinous background, papillary and acinar configurations with vacuolated to granular cytoplasm. The tumor cells may form macro/microcytic, solid, papillary, micropapillary, and tubular structures.[8-11] The tumor cells usually tend to have eosinophilic to vacuolated or "soap-like" cytoplasm and vesicular nuclei with a small prominent nucleolus. The recognition of intraluminal located eosinophilic secretions that are periodic acid-Schiff (PAS) positive and diastase resistant in smears is also crucial to a correct diagnosis.[12,13] In our study, almost all of these characteristic morphological features were present.

One of the striking points is that there is no specific immunstaining for SCs diagnosis yet. Nevertheless, positive staining for protein S-100, vimentin, mammoglobulin, and adipophilin in combination with DOG-1 negativity can be helpful for diagnosis.[13,14]

SC is associated with a specific genetic translocation between chromosomes 12 and 13, t(12;15)(p13;q25), which results in the *ETV6-NTRK3* fusion gene. Determining the translocation by the FISH identification and PCR RT-PCR technique is the gold standard for the diagnosis. However, it is important to keep in mind that this translocation may not be present in each case.[1,12] In our case, we were not able to use these techniques.

SC has overlapping morphological features of the other low-grade salivary malignancies such as adenocarcinoma not otherwise specified, intraductal carcinoma, mucoepidermoid carcinoma, acinic cell carcinoma.[15]

Microscopically, in histopathological diagnosis, SC may show variable patterns such as macro/microcystic, tubular, papillary, etc. Tumor cells are generally expected to have eosinophilic, clear cytoplasm, vesicular nuclei with prominent nucleoli. Another diagnostic tool that can be useful in differentiating this tumor from other neoplasms included in the differential diagnosis is the presence of eosinophilic intraluminal secretions that are PAS positive and diastase resistant. Thus, immunohistochemical staining is essential for diagnosis. Positive immunostaining of S100, SOX-10, GATA-3 with MUC-4, pan-TRK staining coupled with the absence of DOG-1, p63, p40, calponin is a key feature for the diagnosis of the SCs. Furthermore, most SCs have been found to harbor *ETV6-NTRK3* fusions or *ETV6-RET* and *ETV6-MET* fusions.[1,3,12]

On account of many similar features, SCs were previously diagnosed as acinic cell carcinoma. Acinic cell carcinoma still remains the main challenging differential diagnosis. Although lack of cytoplasmic PAS diastase resistant zymogen granules and the positive staining with the NR4A3 and DOG-1 staining are important clues, it is not expected to make the diagnosis of the SCs only with the morphological characteristics without applying immunohistochemistry.[10,12]

Polymorphous adenocarcinoma is another important differential diagnosis. (p63+, SMA+, GATA3-, panTRK-). Another differential diagnosis include mucoepidermoid carcinoma (MEC) (with no S100 and mammaglobin expression) due to both tumors can have intracellular mucin. While there is multivacuolization in SC, univacuolization in MEC can be used for this distinction.[13,15]

Intraductal carcinoma (myoepithelial markers positive and no MUC-4 expression) is another differential diagnosis that should be excluded by additional immunostaining.[15]

We present this case, unlike the literature, the patient was not elderly. Furthermore, cytologic diagnosis can sometimes be challenging because of the heterogeneity of the tumor as we presented. Perhaps the most useful reminder for recognizing SC cytologically is the combination of features of multiple patterns both papillary and cystic areas and the fact

that these features do not completely fit the criteria for either entity. As in our case, the morphological features of the tumor met the defined diagnostic criteria but immunostains should be applied for preventing misdiagnoses. In selected cases, molecular techniques can also be used, confirming the diagnosis which is nowadays accessible to most laboratories. Furthermore, studies with a high level of evidence may provide more accurate information and help clinicians to better understand the clinical behavior and prognosis of this rare entity.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

***Idea/Concept:** İrem Şahver İşgör, Leyla Cinel; **Design:** İrem Şahver İşgör, Leyla Cinel; **Control/Supervision:** Leyla Cinel, Necati Enver; **Data Collection and/or Processing:** İrem Şahver İşgör; **Analysis and/or Interpretation:** İrem Şahver İşgör, Leyla Cinel; **Literature Review:** İrem Şahver İşgör; **Writing the Article:** İrem Şahver İşgör, Leyla Cinel; **Critical Review:** Necati Enver, Leyla Cinel.*

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