Cytopathology

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A Secret Worth Telling: The Salivary Secret (Ory) Affair

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Received: 19 December 2025 | **Revised:** 10 April 2026 | **Accepted:** 26 April 2026

Keywords: salivary gland | secretory | vacuolated

ABSTRACT

Secretory carcinoma (SC) of the salivary gland is a low-grade, slowly growing tumour. However, cytological diagnosis of SC is often challenging due to its morphological mimics. Characteristic cytoplasmic vacuolation seen in SC can be displayed in many tumours. However, careful evaluation of architecture, cytological content and background can assist in a definite diagnosis on FNAC. Application of immunocytochemistry on cell blocks can further aid in diagnosis.

1 | Case

A 24-year-old male presented with a chief complaint of swelling in the left side of the neck below the ear for the last 10 years. The swelling was slowly progressive and painless. On local examination, there was no change in colour and an increase in temperature. Outside imaging studies, Magnetic Resonance Imaging (MRI) was done, which was reported as multiple cervical lymph nodes with a possibility of lymphoma. Following this, fine-needle aspiration cytology (FNAC) was performed at our centre.

Question 1: What is the most probable diagnosis based on the clinical details and photomicrographs of FNA smears (Figure 1)?

A. Mucoepidermoid carcinoma

B. Acinic cell carcinoma

C. Secretory carcinoma

D. Oncocytoma

Question 2: Which of the following rearrangements/translocations will be positive in this case?

A. MYB–NFIB fusion

B. ETV6–NTRK3 fusion

C. MAML2–CRTC1 fusion

D. BRAF V600E mutation

Question 3: Which immunohistochemical profile is typical for the given case?

A. ER+, PR+, HER2−

B. AR+, GCDFP-15+, HER2+

C. S-100+, Mammaglobin+, SOX10+, Pan-TRK+

D. CK5/6+, p63+, EGFR+

Question 4: This tumour closely resembles which carcinoma morphologically and genetically?

A. A Medullary carcinoma

B. Invasive lobular carcinoma

C. Secretory carcinoma of the breast

D. Apocrine carcinoma of the breast

Answers:

Q1. Answer: C. Secretory carcinoma

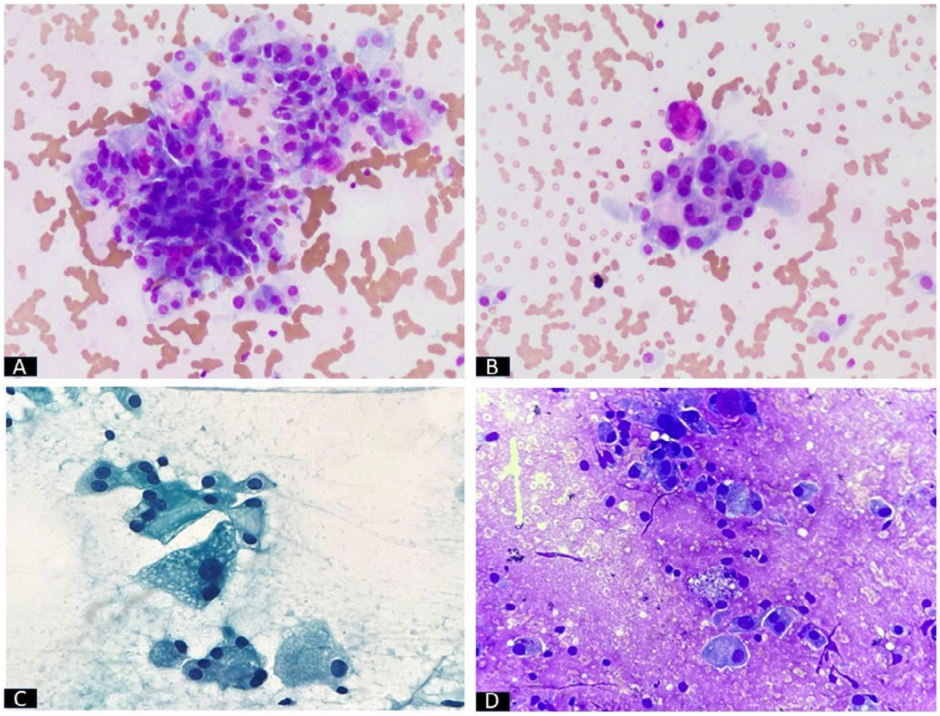

FIGURE 1 | MGG stain: (A: ×20; B: ×40; D: ×40) Clusters and papillaroid fragments of neoplastic cells with vacuolated cytoplasm. In a few cells, intracytoplasmic eosinophilic material is also noted. Pap stain: (C: ×40) Variably sized cells with fine nuclear chromatin and inconspicuous nucleoli.

Q2. Answer: B. ETV6–NTRK3 fusion

Q3. Answer: C. S-100+, Mammaglobin+, SOX10+, Pan-TRK+

Q4. Answer: C. Secretory carcinoma of the breast

2 | Discussion

Salivary gland neoplasms exhibiting clear to vacuolated cytoplasm on fine-needle aspiration cytology (FNAC) represent a morphologically diverse and diagnostically challenging group of lesions. On cytology, such features may be seen in both benign and malignant neoplasms, including acinic cell carcinoma, secretory carcinoma, mucoepidermoid carcinoma and low-grade adenocarcinoma, not otherwise specified (NOS) [1]. This makes a definite diagnosis very difficult. Because clear and vacuolated cytoplasmic patterns overlap among distinct salivary gland tumours, ancillary studies—including special stains, immunocytochemistry and molecular studies correlation are often required to refine the cytological diagnosis and guide appropriate management [1]. The present case of a 24-year-old male with slowly growing infra-auricular swelling presented to OPD with an outside centre MRI. The provisional diagnosis rendered on imaging studies was a lymphoma. Subsequently, FNAC was performed, which revealed cellular smears and showed acinar-like cells arranged in the form of loosely cohesive clusters and nests, as well as scattered singly (Figure 1). These tumour cells were large in size with round, small nuclei having bland chromatin and abundant foamy vacuolated to granular cytoplasm. Many bare nuclei were also noted in the background. The Milan system for Reporting Salivary Gland Cytopathology category VI as malignant was reported. Advice for histopathological examination (HPE) and immunohistochemistry (IHC) was suggested. Following cytological diagnosis, a left conservative parotidectomy was done, and the tumour was excised. The gross examination of the specimen revealed a poorly-circumscribed, unencapsulated lesion measuring 8.0 × 4.5 × 2.5 cm, which was predominantly solid with few cystic areas, and the lesion was completely replacing the normal salivary gland parenchyma and reaching up to the capsule. Grossly matted lymph nodes were yielded. On histopathological examination, a malignant tumour was seen, which was partly circumscribed and showed lobulation. The tumour exhibited microcystic, macrocystic and focal tubular patterns, which were filled with pale eosinophilic colloid-like intraluminal secretions. These cells have monomorphic round vesicular nuclei with small distinct nucleoli and vacuolated to eosinophilic abundant cytoplasm (Figure 2). Lymphovascular invasion and lymph node metastasis with extranodal extension were also identified. Periodic Acid Schiff (PAS) stain was positive for intraluminal secretions and was diastase-resistant. For confirmation of morphological diagnosis. IHC markers S-100 and DOG1 were applied, in which tumour cells revealed cytoplasmic positivity for S-100, while DOG1 was negative. The main cytologic differentials for secretory carcinoma include acinic cell carcinoma, mucoepidermoid carcinoma, low-grade adenocarcinoma not otherwise specified (NOS), and oncocytic tumour, as discussed in Table 1 [2, 3]. Acinic cell carcinoma (AciCC) is the most common diagnostic pitfall. It shows cells with basophilic granular cytoplasm due to zymogen granules arranged in microacinar

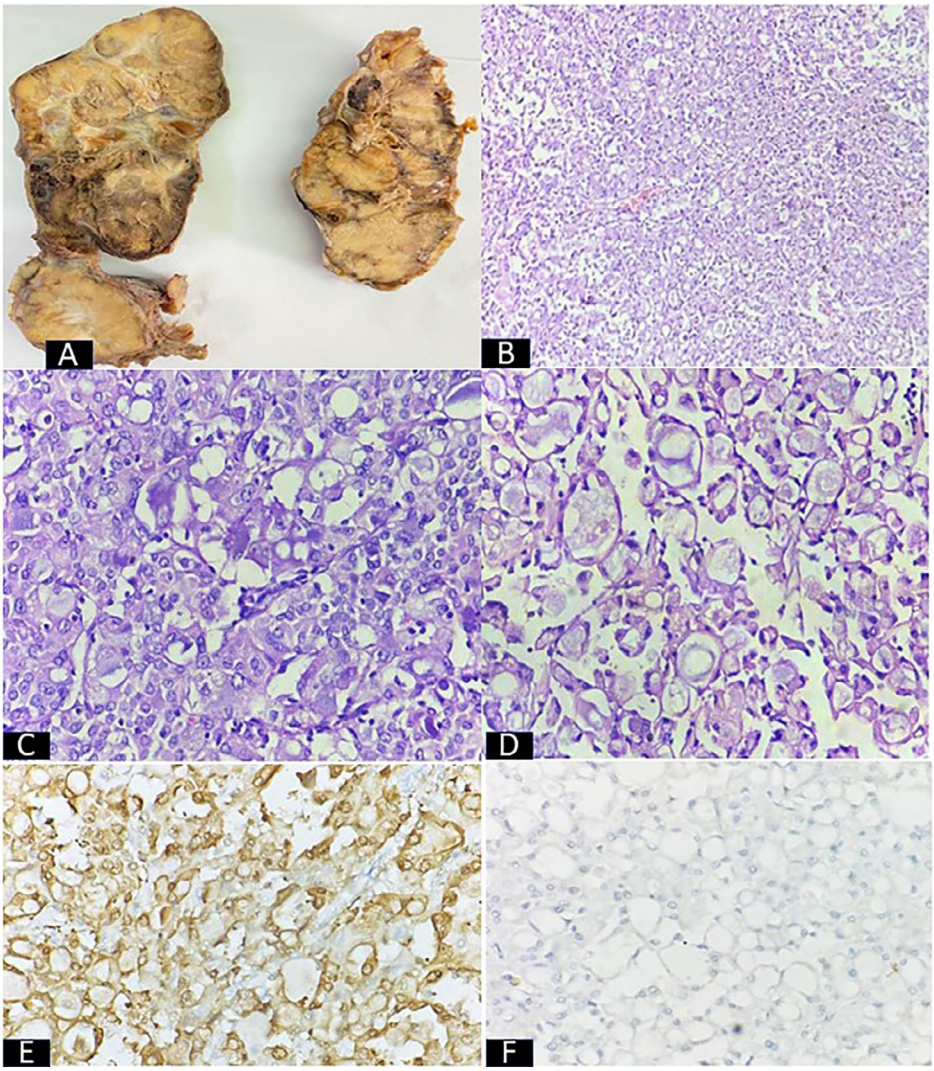

FIGURE 2 | (A) Gross of the cervical mass showing a multilobulated mass with infiltrative margins. The cut section was greyish brown. H&E section: (B: ×10; C: ×40; D: ×40) Tumour was composed of a diffuse sheet with cystic, microcystic and tubular patterns. Tumour cells were moderately pleomorphic with vesicular chromatin and abundant vacuolated cytoplasm. (E) S100 IHC showing diffuse cytoplasmic positivity in the tumour cells. (F) DOG1 IHC marker is diffusely negative in the tumour cells.

patterns. However, these granules differ from the vacuolated cytoplasm of secretory carcinoma, and the background lacks eosinophilic secretory material. Immunohistochemically, AciCC is DOG1 positive and mammaglobin negative, unlike SC [4, 5]. Mucoepidermoid carcinoma (MEC) can mimic SC when mucin is abundant. MEC smears display a mixture of mucinous, intermediate and squamous cells along with mucin pools and necrosis. The cells are more pleomorphic, and there is no uniform vacuolated population. MEC typically lacks coexpression of S100 and mammaglobin [6]. Low-grade adenocarcinoma NOS may show bland cytology but lacks the characteristic secretory background and molecular signature of SC. Similarly, oncocytoma contains cells with dense, granular cytoplasm rich in mitochondria, but no vacuolation or secretory material, which helps distinguish them from SC [2, 3]. Though in challenging cases, histopathology and even molecular tests are needed for further confirmation. The demonstration of the *ETV6-NTRK3* gene fusion provides definitive confirmation. Awareness of its morphologic spectrum and common diagnostic mimics of salivary gland neoplasm with vacuolated cytoplasm is crucial to prevent misdiagnosis. A cytological algorithm, along with ancillary investigations, can be of help (Figure 3). Given its generally favourable prognosis and potential for targeted therapy, accurate cytologic recognition of secretory carcinoma has significant clinical relevance.

TABLE 1 | Differentiation of salivary gland carcinomas with vacuolated/secretory morphology.

Tumour subtype	Cytology	Immunohistochemistry (IHC) profile for cell block	Genetic alteration
Secretory carcinoma [4, 6]	Papillary, tubular; eosinophilic secretions; vacuolated cytoplasm	S-100+, Mammaglobin+, SOX10+, CK8/18+, EMA+, Pan-TRK+; DOG1−	ETV6–NTRK3 fusion (t(12;15))
Acinic cell carcinoma [3, 4]	Predominantly acinar pattern; basophilic cytoplasm; cytoplasmic zymogen granules	DOG1+, NR4A3+; usually S-100−, Mammaglobin−; SOX10 variable	NR4A3 rearrangement (most cases)
Mucoepidermoid carcinoma [1, 2]	Mixture of mucinous, epidermoid and intermediate cells; with evidence of cystic changes and background fluid	CK5/6+, p63+, MUC1+, MUC5AC+; often S-100−, Mammaglobin−	MAML2–CRTC1/3 fusion
Oncocytoma [5]	Large polygonal cells with abundant granular eosinophilic cytoplasm (mitochondria-rich)	Mitochondrial markers+, CK7+, EMA+; usually S-100−, Mammaglobin−	No specific recurrent translocation

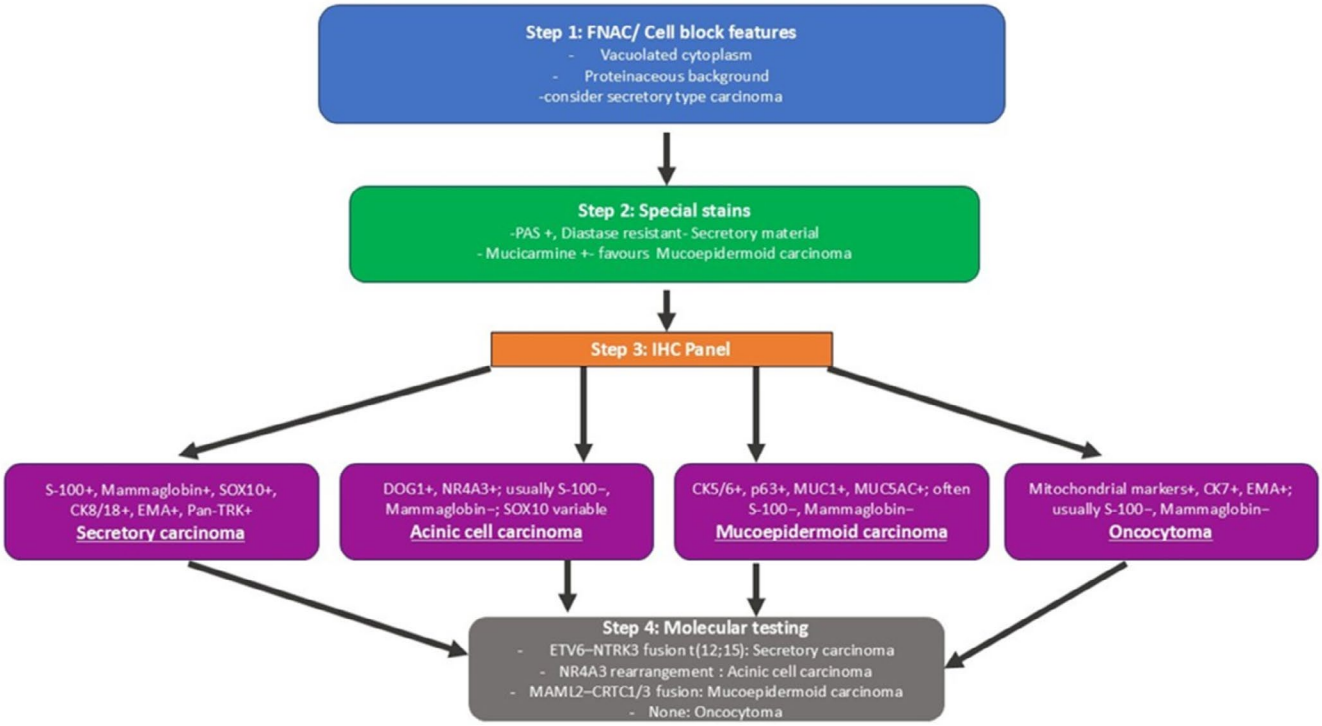

FIGURE 3 | Algorithm for the diagnostic approach to tumours with vacuolated cytoplasm in the salivary gland.

Author Contributions

M.S.: conceptualization, drafting and editing the manuscript. M.Y.: involved in diagnosis, drafting and data collection. S.S.B.: reviewing the manuscript. S.C.: diagnosis and reviewing the manuscript. Each author has participated in the work and takes responsibility for the content of this article. All authors read and approved the final manuscript.

Acknowledgements

The authors are thankful to the technical staff of the histology lab for assisting us in ancillary tests.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

No data were generated from the current study. Required information can be produced by the corresponding author if needed.

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