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(CASE REPORT)

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Diagnosis of mammary analogue secretory carcinoma of the parotid gland by cytology material: Case report of a rare tumor and a brief review of the literature

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Abstract

Mammary analogue secretory carcinoma (MASC) is a low-grade malignant tumor of the salivary glands that is often mistaken for other tumors. MASC also displays similar characteristics of mammary secretory carcinoma, including the gene fusion of ETV6-NTRK3. The confirmed location of MASC as a primary tumor of the salivary gland makes the distinction from mammary secretory carcinoma.

MASC most commonly presents as a painless, slow-growing mass, most often in the parotid gland. Although complete surgical resection results in a good prognosis, more aggressive variants with metastatic potential are reported. The radiologic and clinical presentation is often nonspecific and can resemble benign lesions, thus necessitating tissue diagnosis with immunohistochemistry (IHC) and molecular studies. Our case illustrates that fine-needle aspiration (FNA) cytology material alone can provide a definitive diagnosis of MASC and a management plan.

The typical cytohistomorphologic features are evident in adequately sampled FNA material, and IHC usually shows S-100 and mammaglobin expression and DOG-1 negativity. The final confirmation is reached through the detection of the ETV6-NTRK3 fusion gene through FISH. This case highlights the importance of a multimodal diagnostic strategy, which allows confirmation of the diagnosis of MASC with high reliability using FNA cytology and ancillary studies. The identification of the ETV6-NTRK3 translocation not only confirms the disease but also provides an opportunity for therapeutic targeting. Surgical resection with clear margins is the primary treatment, which provides long-term disease-free survival in most patients with no adjuvant therapy. We have noted how preoperative FNA cytology can help in making the best surgical decisions and providing good outcomes.

Keywords: Breast; Salivary glands; Immunohistochemistry; Molecular

1. Introduction

Mammary analogue secretory carcinoma (MASC) is a low-grade malignancy occurring in the salivary glands. [1] There are striking similarities in this type of tumor to mammary secretory carcinoma in three aspects, namely cellular morphology in microscopic observations, the pattern of immune markers, and the genetic features. Both tumor types are associated with ETV6-NTRK3 gene fusion. Distinction between the two tumors is achieved by confirming their location, whether it is the breast, or the salivary glands. [2]

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MASC was first described as a unique tumor in 2010, and has posed serious diagnostic difficulties to pathologists. The clinical presentation and microscopic appearance of the tumor are very similar to more frequent salivary gland malignancies, namely acinic cell carcinoma (AcCC) and mucoepidermoid carcinoma (MEC). [3] [4] [5]

Although MASC has a unique molecular signature with its ETV6-NTRK3 gene fusion, it may not be sufficient for diagnostic clarity. The clinical, behavioral, and morphological overlap with other neoplasms in the salivary glands still makes identification of MASC a complicated process that necessitates consideration of numerous diagnostic parameters. [2] Although ETV6-NTRK3 gene fusion is observed in more than 90% of MASC cases, other molecular findings have been identified. [5]

The necessary role of ancillary studies, including IHC and molecular studies, cannot be overstated in the diagnosis of MASC. Such techniques are important not only to differentiate MASC from its histologic mimickers by characterizing the typical immunoprofile but also, and most importantly, the pathognomonic ETV6-NTRK3 gene rearrangement. [2]

Moreover, this case illustrates that adequately sampled FNA cytology, resulting in a cell block, can offer sufficient material for a full and accurate preoperative diagnosis of MASC, with the performance of ancillary studies. This is essential for appropriate surgical planning and patient counseling. [6] Raising the awareness of clinicians and pathologists to this rare tumor is important so they consider it early in the differential diagnosis of the salivary gland and neck masses. The increased recognition of this rare tumor, with a thorough understanding of its clinical presentation, cytological morphology, and molecular pathology, will enable an earlier and more accurate diagnosis. The future for MASC diagnosis and treatment is bright, and advances in molecular research, the advent of artificial intelligence (AI) in pathology, and other evolving technologies will provide even better diagnostic accuracy and pave the way toward more tailored and personalized treatments.

2. Case presentation

A 42-year-old male presented with a gradually increasing painless lump in the left side of the preauricular area (In front of and below the left ear). It was observed approximately seven months previously, and during that time, the lesion was asymptomatic and developed so slowly that the patient did not seek medical assistance in time.

However, it was in the last few weeks that its size had markedly increased, so the patient decided to seek medical attention. In combination with this, the patient also experienced difficulties with swallowing and with opening his mouth wide, in addition to occasional numbness on the left part of his face. He also complained of unequal salivary fluctuations, which ranged from hyper salivation to dryness. He denied any pain, fever, constitutional symptoms, or a history of cancer in the family. Physical examination revealed a firm to hard left preauricular area mass approximately 1.8 cm, partially movable, but fixed to the deeper tissues to some degree. The overlying skin was slightly inflamed, and there was no sign of lymphadenopathy in the region.

Lab tests and systemic review were noncontributory. The early clinical diagnostic considerations were those of a pleomorphic adenoma, other benign or malignant salivary gland tumors, or chronic sialadenitis. The rubbery firmness and absence of systemic symptoms did not point to lymphoma. The imaging exams, including ultrasound, CT, and MRI, showed a clear, oval 1.8 cm mass in the parotid gland, mostly cystic, with lobulated borders and without local invasion. The radiologic appearance was consistent with a benign salivary tumor, such as pleomorphic adenoma or cystadenolymphoma (Warthin's tumor), but was not specifically diagnostic.

Since tissue diagnosis was still required, and considering the availability of a well-supported cytopathology service, a fine needle aspiration (FNA) was performed. The FNA material was adequate to prepare a cell block for IHC studies and molecular analysis if needed. The FNA smears were moderately cellular with cohesive clusters and flat sheets of uniform epithelial cells. Papillary structures with a thin fibrovascular core were also present, as well as acinar-like patterns and microcystic spaces, some of which were filled with pink eosinophilic secretions. The individual cells had low-grade nuclear appearance, including small, round to oval nuclei, smooth nuclear membrane, fine chromatin, and small nucleoli. Cytoplasm was abundant and eosinophilic; many showed foamy and vacuolated features. There was mucinous colloid-like material in many regions. The background was cystic and proteinaceous. Histologic microscopic examination of the cell block revealed a neoplasm with a varied architectural pattern comprising solid, microcystic, tubular, papillary, and cribriform areas. The most notable was the luminal spaces with colloid-like, eosinophilic secretions, which were like the FNA smear appearance. The nuclear morphology was low grade, and no mitoses, necrosis, or pleomorphism was observed. (Figure 1 A, B, C, D)

The cytologic and histologic appearance were used to include the differential diagnosis of acinic cell carcinoma (AcCC), mucoepidermoid carcinoma (MEC), low-grade adenocarcinoma, and mammary MASC. Since these entities have been documented to exhibit similar cytohistologic features, IHC studies were imperative to further evaluate and definitively diagnose the tumor.

IHC analysis of the cell block was positive for S-100 protein, mammaglobin, and PAS-diastase and negative for DOG-1, p63, SMA, and myoepithelial/basal cell differentiation markers. There were no zymogen granules. This immunoprofile was strongly consistent with MASC. It effectively excluded both AcCC (which is usually DOG-1 positive with zymogen granules) and MEC (which has a mixed mucous and epidermoid pattern). Molecular analysis was completed to confirm the diagnosis and determine possible therapeutic target management. The definitive diagnosis was made as the diagnostic ETV6-NTRK3 fusion gene was identified by fluorescence in situ hybridization (FISH).

A whole-body scan demonstrated no metastatic disease or local aggressive infiltration on staging workup. The patient then had total surgical removal of the parotid gland and the soft tissue margins around it. The 1.8 cm mass was completely excised with adequate negative margins. The previous cytologic and molecular results were proved to be correct; the histopathologic analysis showed a low-grade MASC with no necrosis, no perineural or lymphovascular invasion, no nodal involvement, no local aggressive invasion, and no signs of high-grade transformation. (Figure 1 A, B, C, D)

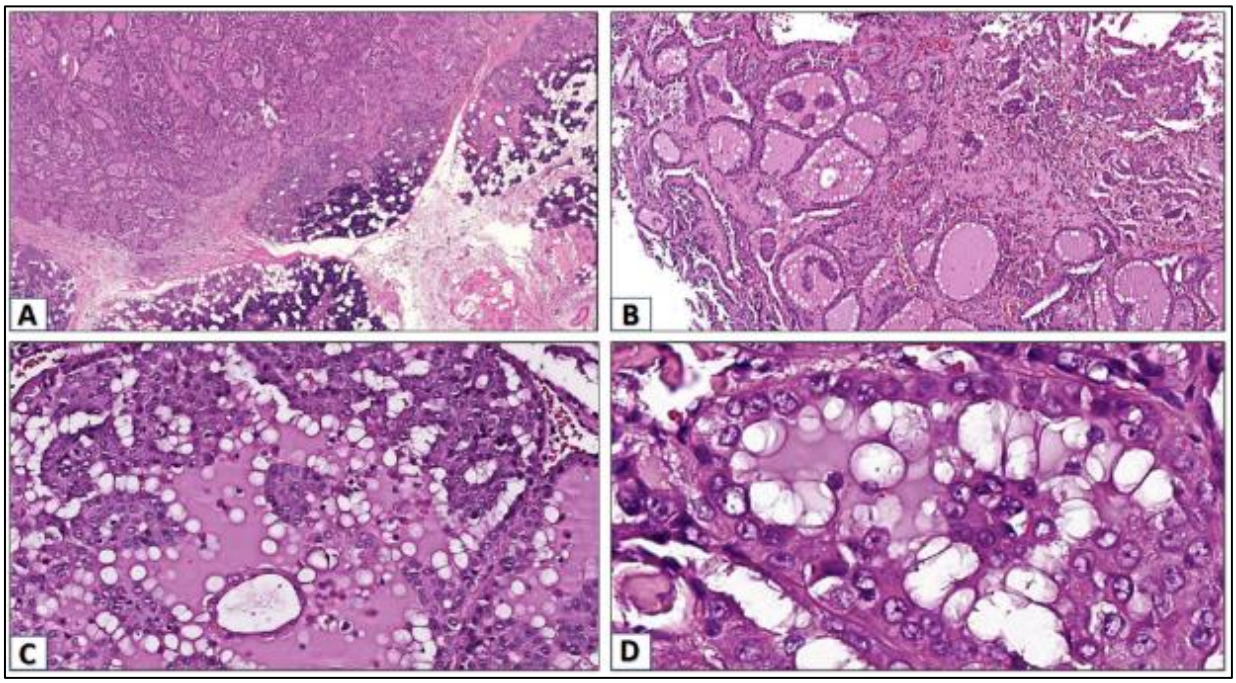

Figure 1 Histomorphology of the excised mammary analog secretory carcinoma (MASC)

1A Low power view showing the tumor infiltrating the salivary gland, displaying a spectrum of architectural morphology (H&E stain X20); 1B: Intermediate power view showing solid sheets of tumor cells and dilated tubular structures filled with pink eosinophilic secretions (H&E stain X40); 1C: Intermediate power view showing papillary structures protruding into the dilated ducts (H&E stain X40); 1D: High power view showing large vacuolated cells with bland nuclei showing minimal atypia and no mitosis (H&E stain X60)

The postoperative recovery was uneventful. Because of the low-grade characteristic of the tumor and lack of risk factors, no adjuvant treatment, either radiation or targeted therapy, was required. The follow-ups were arranged at increasing intervals over time. There was no sign of recurrence, metastasis, or return of the salivary gland symptoms within four years of clinical and imaging monitoring. The patient was kept free of disease, with preservation of functional quality of life.

This case demonstrates that FNA cytology is a very useful diagnostic tool in the diagnosis of MASC, especially when cell block preparation, IHC, and molecular studies are used. Although the cytologic characteristics of MASC can resemble other salivary gland neoplasms, with a thorough examination, early suspicion of the tumor, and further confirmatory IHC and molecular testing, an accurate diagnosis can be achieved. Notably, the capacity to make a confident preoperative diagnosis enabled proper surgical planning, facilitated proper patient counseling, and eliminated the need for diagnostic

excision and staging procedures. Moreover, the recognition of the ETV6-NTRK3 fusion is therapeutically relevant in advanced or recurrent illness, and this provides possible options for targeted therapy. Surgical management, in the present case, was, however, curative.

3. Discussion

3.1. Background (History, epidemiology, risk factors, and WHO classification)

Mammary analogue secretory carcinoma (MASC) is a unique and comparatively new type of salivary gland tumor. Described in 2010, MASC was first recognized because of its strong histological similarity to secretory carcinoma of the breast, a tumor that shares a rare ETV6-NTRK3 gene fusion with MASC. This is a molecular signature that is now a hallmark of definitive diagnosis of MASC. [4] [5] [6] Prior to its formal characterization, it is likely that there were many cases of MASC misclassified as other salivary gland tumors, including acinic cell carcinoma or mucoepidermoid carcinoma. Thus, there is a need to develop advanced methods of diagnostic testing to identify MASC accurately. MASC is a rare tumor, which represents a small number of all salivary gland malignancies; it is estimated that less than 0.3% of all salivary gland malignancies are MASC. [5] It may be manifested in a broad age group, both in pediatric and adult patients, with no gender preference. Although age, radiation exposure, smoking, and a family history of cancer are general risk factors of salivary gland cancers, an established risk factor specific to MASC is yet to be clearly identified. [2] Additional studies are underway to clarify any special predisposing factors to this type of tumor.

The WHO Classification of Head and Neck Tumors has been instrumental in the standardization of the nomenclature and classification of MASC. In the 4th edition (2017), MASC was recognized as a distinct entity, with the nomenclature changed to secretory carcinoma of the Salivary Gland (SCSG). It was just a change of name, not in classification. The new name was retained in the recent WHO update 2022. However, the old term MASC is still commonly used in the medical literature. The classification has evolved to standardize the terminology and avoid confusion with breast cancer, from which the "mammary analog" part of the original name derived. [8] In this report, we are using the term “MASC” as most clinicians are familiar with this term.

4. Clinical presentation and imaging findings

Mammary analog secretory carcinoma (MASC) is typically seen in adults occurring between the ages of 40-50 years, although this has been seen in a broad range of ages, including children and older patients. [9] [10] The prevalence is a little higher in males, but the incidences are balanced between the genders with reported gender ratios of 1.02:1 to about 1.5:1. [11] Occurrence is most frequently seen in the parotid gland (~56-70% of cases), then in the submandibular gland, the soft palate, the buccal mucosa, the lip, and the tongue base. [9] [10] A painless but slowly enlarging mass is frequently reported by the patients and may be detected during a routine physical examination or incidentally. [10] [12]

Although most patients are asymptomatic, some might experience facial numbness, difficulty opening the mouth or swallowing, or irregular flow of saliva in cases where the tumor presses against nearby structures. [12] Pain, ulceration, or rapid growth is uncommon and usually indicates high-grade transformation or late presentation. [13] The course of the illness is usually long, often several years (median about 4.25 years), with the reported range being 2 months to 30 years. There are rare cases of rapid tumor growth, which is, however, atypical and presents with regional metastasis and poor prognosis. The size of the tumor at the time of diagnosis is usually between 0.5 cm and ~5.5 cm, with an average of 2.1 cm; some studies indicate a range of 0.3-8.5 cm. [10] [12] [14] The tumor in our case was 1.8 cm. Typical imaging characteristics of these lesions include a well-circumscribed, partially cystic, or mixed solid-cystic mass that may contain internal septations. [12] [15] On ultrasound, the lesions can be hypoechoic and solid; contrast-enhanced CT can demonstrate a well-defined, mildly enhancing mass; MRI may present T1 hyperintensity and variable T2 signal, including hyperintense cystic areas. [12] [15]

The imaging features of a clear, oval 1.8 cm mass in the parotid gland, mostly cystic with lobulated borders and without local invasion, are in line with the overall radiologic presentation of MASC. However, it is necessary to mention that imaging can only define the size, location, and the general appearance of the mass, but is rarely conclusive in MASC because it mimics other salivary gland neoplasms. [16] Thus, imaging is used mainly as a localization tool that serves to orient further diagnostic techniques, including fine needle aspiration, and not as a determining factor of the diagnosis.

4.1. Pathology (Cytology and cell block, microscopic findings, Immunohistochemistry, and molecular studies)

Imaging studies (ultrasound, CT, and MRI) commonly reveal a well-defined and oval-shaped mass with lobulated borders without signs of local invasion. The radiologic appearance is usually typical of a benign salivary tumor, e.g.,

pleomorphic adenoma or cystadenolymphoma (Warthin's tumor); however, the diagnosis was not conclusive in most cases. [17] Because tissue diagnosis will still be required, a fine needle aspiration (FNA) is carried out if an advanced cytopathology service is available, or a tissue biopsy is performed.

Typical features of FNA smears include moderately cellular, cohesive clusters and flat sheets of monotypic epithelial cells. Specifically, papillary structures with thin fibrovascular cores, and acinar-like structures and microcystic spaces, some with pink eosinophilic secretions, are observed. The single cells show low-grade nuclear atypia, characterized by small, round-oval nuclei, smooth nuclear membranes, fine chromatin, and small nucleoli. Cytoplasm is rich, eosinophilic, foamy, and vacuolated. In certain places, mucinous or colloid-like material is abundant. [18] [19] Our case displayed most of these described features. Cytology FNA material can be highly diagnostic if sampling is successful, enabling the production of a paraffin cell block for all required IHC and molecular studies, as in our patient's case. Although all required studies can be performed on destained cytology slides, the results are more accurate on a paraffin cell block. [19]

In our case, a cell block was made, and the cytologic and histologic features suggested that the possible diagnoses were acinic cell carcinoma (AcCC), mucoepidermoid carcinoma (MEC), low-grade adenocarcinoma, and mammary analogue secretory carcinoma (MASC). These can have overlapping cytomorphologic features, but IHC studies and the diagnostic MASC fusion gene ETV6-NTRK3 were identified, thus confirming the diagnosis.

5. Management and Outcomes

Surgical resection is the primary and most effective treatment of mammary analogue secretory carcinoma (MASC) of the salivary glands. Because of its generally low-grade nature and indolent clinical behavior, it is often cured by complete surgical excision with sufficient negative margins, as was the case with our presented case. [12] The degree of surgical management varies according to the size, location, and involvement of surrounding structures. In the case of parotid gland tumors, this usually entails the partial/complete removal of the parotid gland, as was the case with our patient. [20] [21]

The use of adjuvant therapy, including radiation or chemotherapy, in MASC is usually restricted and dependent on the presence of high-risk characteristics. Such risk factors are positive surgical margins, perineural or lymphovascular invasion, nodal involvement, high-grade transformation, or extensive local aggressive invasion. [22] Without the presence of these features, as in our patient who did not have any adverse pathological findings and a clear margin, adjuvant treatment is not normally necessary. This strategy is in line with the existing knowledge that MASC, especially low-grade tumors, have a good prognosis with surgery alone. [20] [21] The ETV6-NTRK3 fusion gene, although diagnostic, also has a potential specific target for therapy, which can be considered in the case of advanced, recurrent, or metastatic disease, where surgical treatment is not feasible. [2]

The prognosis of patients with MASC is usually good, particularly those with low-grade tumors that were completely removed. Recurrence rates are low, and the disease-free survival rates are high. It is important to follow up regularly, by clinical examination and imaging, to check against any evidence of recurrence or metastasis, which reduces significantly with time. The four-year disease-free survival of our patient with maintenance of functional and quality of life further highlights the excellent outcome of prompt and proper surgical treatment of MASC. [6] [15]

Our patient had an uneventful postoperative course. As the tumor was low grade and had no risk factors, such as positive surgical margins, nodal involvement, or aggressive features, no adjuvant therapy, such as radiation or targeted treatment, was necessary. Follow-ups with ever-increasing intervals were to be performed. There were no recurrences, metastasis, or new salivary gland symptoms at 4 years of clinical and imaging follow-up. The patient has been in clinical remission with no deterioration of function and quality of life.

5.1. Pathogenesis and Pathophysiology

MASC is invariably associated with a recurrent translocation that is the fusion of two genes, t(12;15) (p13;q25), resulting in the fusion of the ETV6 gene with the gene, NTRK3, forming the hybrid gene, ETV6-NTRK3. This fusion gene serves as the molecular signature of MASC and is important for definitive diagnosis. The ETV6 gene, a transcription factor, is normally located on chromosome 12. [2] Mutations in the NTRK3 gene, located on the 15th chromosome, cause the body to produce tyrosine kinase receptor proteins. [23] The ETV6-NTRK3 fusion protein is a singular abnormal tyrosine kinase, which is constitutively activated in the absence of a ligand. A similarity is that the fusion partner of ETV6 (33-ETS transcription factor) has a dimerization domain that enables dimerization of two ETV6-NTRK3 proteins, which is the prerequisite for kinase activation of the NTRK3 component. It is these unconstrained activities that drive

continuous activation of downstream signaling pathways, such as the MAPK/ERK and PI3K/AKT pathways. These pathways will activate and lead to pathological cell growth, survival, and differentiation, ultimately leading to cancer development. [1] [2] [24]

Since the ETV6-NTRK3 fusion gene is the direct cause of the development and advancement of MASC, it is considered an oncogenic driver. [24] This knowledge of molecular pathology not only provides the biological explanation of the disease but also offers a possible treatment. By inhibiting the activity of the NTRK3 kinase, physicians will be able to prevent the action of the driving force of the cancer, which can be a feasible treatment option, particularly for advanced or recurrent patients.

5.2. What Have we Learned from this Case?

This example of mammary analogue secretory carcinoma (MASC) of the salivary gland has several learning points to offer. First, it highlights the changing context of salivary gland tumor diagnostics, wherein classic clinical and imaging manifestations, although essential in the initial evaluation, are frequently non-diagnostic. The slow course and diverse appearance of MASC require a great deal of suspicion, particularly in the case of a slowly growing painless swelling in the parotid region. Secondly, the case shows the importance of a broad-based diagnostic process. FNA cytology, when augmented by cell block, IHC, and molecular testing, can be a useful tool for accurate preoperative diagnosis. The capacity to detect the typical ETV6-NTRK3 fusion gene is critical, both to provide a definitive classification and to inform treatment strategy, including the possibility of targeted treatments in late-stage cases. This combined diagnostic route reduces the incidence of misdiagnosis and eliminates unnecessary or delayed treatment.

This case, lastly, supports the overall positive prognosis of MASC, especially when detected at an early stage and treated through complete surgical excision. In the case of this patient, due to the absence of high-risk factors, the adequate therapy for the disease consisted of curative surgery alone. That produced an excellent prognosis.

6. Conclusion

The case report of mammary analogue secretory carcinoma (MASC) of the salivary gland is an important contribution to the current body of knowledge, firstly because of the detailed account of the diagnostic process and its effective treatment of this uncommon entity. We present this case to highlight the growing awareness of MASC, especially its insidious clinical manifestation and the diagnostic dilemma that can be presented by its morphological resemblance to more prevalent salivary gland tumors. The effective and accurate preoperative diagnosis that was made possible by integrating fine needle aspiration cytology, advanced IHC, and a definitive molecular identification of the ETV6-NTRK3 fusion gene demonstrates the paramount importance of a multidisciplinary approach in the diagnosis.

Moreover, this case demonstrates a positive prognosis of MASC when correctly diagnosed and treated by complete surgical removal, even without adjuvant treatment. By describing the uneventful recovery of the patient and his disease-free survival for several years, we aim to emphasize the clinical importance of early and correct diagnosis as the key to maximizing patient outcomes. This report helps to increase awareness among clinicians and pathologists, recommending an increased index of suspicion and prudent use of ancillary tests to achieve accurate classification and individualized management of MASC.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors make the following declarations:

- **Payment/services information:** All authors have declared that they received no financial support from any organization for the submitted work.

- **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might be interested in the submitted work.

Statement of ethical approval

Ethical review and approval were not required for this study involving human participants. The paper has been sufficiently anonymized to maintain the patient's confidentiality.

Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

Statement of informed consent

The patient was lost to follow-up, and all attempts to reach the family members were unsuccessful. Therefore, the paper has been sufficiently anonymized to maintain patient confidentiality.

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