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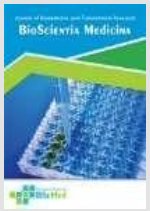

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Intraoperative Frozen Section Diagnosis of Adenoid Cystic Carcinoma of the Minor Salivary Gland: A Case Report

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A B S T R A C T

Background: Adenoid cystic carcinoma (ACC) is a rare malignant tumor of the salivary glands known for its slow growth, invasive behavior, and propensity for perineural invasion. The diagnosis of ACC can be challenging, especially during intraoperative frozen section consultation. This case report highlights the crucial role of frozen section diagnosis in guiding surgical management and ensuring tumor-free margins, which are critical for patient prognosis. **Case presentation:** A 44-year-old male presented with a slow-growing, occasionally painful nodule on his upper lip, without facial numbness or other systemic symptoms. A frozen section examination was performed intraoperatively to assess the lesion and determine the margin status. The frozen section revealed malignancy, characterized by tumor cell proliferation in tubular, cribriform, and solid patterns, all hallmarks of ACC, along with perineural invasion. A wide excision was performed, and subsequent frozen sections of the surgical margins confirmed they were free of tumor. The diagnosis of ACC was confirmed on histopathological examination of the paraffin block. **Conclusion:** This case underscores the importance of frozen section diagnosis in the management of ACC of the minor salivary glands. The accurate assessment of the lesion and margin status during surgery allows for appropriate surgical decision-making, ensuring complete tumor removal and minimizing the risk of recurrence.

1. Introduction

Adenoid cystic carcinoma (ACC) is a rare but significant malignancy that arises from the secretory glands, most commonly affecting the major salivary glands like the parotid and submandibular glands. However, it can also originate in the minor salivary glands dispersed throughout the oral cavity, sinonasal tract, and other exocrine glands. ACC is notorious for its indolent growth pattern, often spanning years before detection. Despite this slow initial progression, it exhibits a propensity for local invasion, frequently extending into surrounding tissues, including bone and nerves. This insidious growth pattern contributes to the challenges of achieving complete surgical resection and managing the disease effectively. The hallmark of ACC is its diverse histologic patterns, encompassing cribriform, tubular, and solid configurations. The cribriform pattern, often referred to as the "Swiss cheese" appearance, is characterized by cylindrical tumor cells arranged around acellular spaces. These spaces contain a variety of extracellular matrix components, including basement membrane-like material and glycosaminoglycans. The tubular pattern features duct-like structures lined by cuboidal or columnar epithelial cells, reminiscent of normal glandular architecture. In contrast, the solid pattern presents as sheets or nests of basaloid cells with minimal extracellular matrix. The proportion of these patterns can vary within a single tumor, adding to the complexity of diagnosis and treatment planning.[1-3]

Perineural invasion (PNI) is a defining characteristic of ACC, underscoring its neurotropic

behavior. Tumor cells have an affinity for invading nerves, often extending along the perineural spaces. This phenomenon is associated with a higher risk of local recurrence, distant metastasis, and increased mortality rates. The exact mechanisms underlying PNI in ACC remain an area of active research, but it is believed to involve complex interactions between tumor cells and the microenvironment within the nerves. The clinical presentation of ACC is variable and depends on the tumor's location and extent. In the salivary glands, it typically manifests as a slow-growing, painless mass. However, as the tumor progresses, it can cause pain, facial nerve paralysis, or difficulty swallowing. In other sites, such as the sinonasal tract, symptoms may include nasal obstruction, epistaxis, or proptosis. Due to its nonspecific presentation, ACC is often misdiagnosed or diagnosed at an advanced stage, highlighting the need for increased awareness and prompt diagnostic evaluation. The diagnosis of ACC relies on a combination of clinical, radiologic, and histopathologic findings. Imaging studies, such as computed tomography (CT) and magnetic resonance imaging (MRI), are crucial for assessing the tumor's size, location, and extent of invasion. However, the definitive diagnosis is established through histopathologic examination of a biopsy specimen. The pathologist evaluates the cellular morphology, growth patterns, and presence of PNI to confirm the diagnosis.[4-7]

The treatment of ACC typically involves a multidisciplinary approach, with surgery being the mainstay of therapy. The goal of surgery is to achieve complete tumor removal with negative margins, minimizing the risk of local recurrence. However, due to the infiltrative nature of ACC and its propensity for PNI, achieving wide surgical margins can be challenging. In cases where complete resection is not feasible or when there is a high risk of recurrence, adjuvant radiotherapy is often recommended. Chemotherapy has a limited role in the treatment of ACC but may be considered in patients with advanced or metastatic disease. The prognosis of ACC is variable and depends on several factors, including the tumor's location, stage, histologic grade, and presence of PNI. Despite advances in treatment, ACC is known for its late recurrence and propensity for distant metastasis. Long-term follow-up is essential to monitor for recurrence and manage potential complications.[8-10] In this case report, we present a case of ACC arising in the minor salivary gland of the upper lip. The patient presented with a slow-growing nodule, and the diagnosis was established through an intraoperative frozen section examination.

2. Case Presentation

This report details the case of a 44-year-old male who presented with a slow-growing nodule on his upper lip. The patient provided a history of a slow-growing nodule on his upper lip that had been present for approximately two years. He reported occasional pain in the nodule but denied experiencing any facial numbness, paresthesia, fever, or weight loss. There was no history of similar illnesses or prior radiation therapy. The patient was referred from another hospital where a suspicion of malignancy had been raised. This initial history is crucial in directing the diagnostic process. The slow-growing nature of the lesion is a characteristic often associated with salivary gland tumors, including both benign and malignant types. However, the presence of occasional pain raises the suspicion of a malignant process, as benign lesions are typically painless. The absence of neurological symptoms, such as facial numbness or paresthesia, suggests that the lesion may not have yet involved critical facial nerves. However, this does not rule out the possibility of perineural invasion, a hallmark of adenoid cystic carcinoma (ACC), which can occur even in the absence of overt neurological deficits. The lack of systemic symptoms like fever or weight loss is also noteworthy. While these symptoms can be associated with malignancy, their absence in this case may indicate an early stage of disease. However, it is essential to consider that ACC is known for its indolent growth pattern and can remain asymptomatic for extended periods. The referral from

another hospital with a suspected malignancy diagnosis highlights the need for a comprehensive evaluation to confirm the diagnosis and guide appropriate management. Physical examination revealed a nodule with slight ulceration on the upper lip. The nodule measured approximately 3 x 2 x 1 cm and exhibited a firm consistency with indistinct borders. Palpation elicited slight pain. No palpable lymph nodes were detected in the neck. The presence of ulceration on the nodule is concerning, as it can be indicative of a malignant process. Ulceration may arise from the tumor outgrowing its blood supply, leading to tissue necrosis and breakdown. The firm consistency of the nodule is also suggestive of malignancy, although some benign lesions can also present with a firm texture. The indistinct borders raise the possibility of local invasion into surrounding tissues, a feature commonly observed in ACC. The absence of palpable lymph nodes in the neck is relatively reassuring, suggesting that the disease may be localized. However, it is important to note that the absence of clinically detectable lymph node metastasis does not definitively exclude the possibility of microscopic spread. No radiological abnormalities were detected on chest radiography. Ultrasound examination of the neck revealed no abnormalities in the thyroid or lymphadenopathy in the neck or preauricular regions. The normal chest radiography findings suggest that the disease is likely localized and has not metastasized to the lungs, a common site of distant spread for ACC. The absence of thyroid abnormalities or cervical lymphadenopathy on ultrasound further supports the possibility of localized disease. However, it is crucial to acknowledge that imaging studies have limitations in detecting microscopic disease or subtle areas of invasion. Based on the anamnesis, clinical findings, and imaging results, the initial clinical diagnosis was malignancy of the salivary gland. This initial diagnosis provides a working hypothesis for further investigation and management. However, it is essential to emphasize that a definitive diagnosis can only be established through histopathological examination. The clinical features and imaging findings are suggestive of a malignant salivary gland tumor, but they cannot differentiate between various types of salivary gland malignancies. Therefore, a biopsy is necessary to confirm the diagnosis and determine the specific histologic subtype, which is crucial for guiding treatment decisions and predicting prognosis (Table 1).

To further evaluate the lesion and guide surgical management, a comprehensive examination was undertaken, encompassing macroscopic assessment, imprint cytology, and intraoperative frozen section analysis. Gross examination of the excised tissue revealed a reddish-white, rubbery, solid specimen measuring 3 x 2 x 1.5 cm. An ulceration with a diameter of 0.5 cm was observed on the skin surface. On cross-section, a solid white mass with a diameter of 2.5 cm was identified, with an unclear capsule (Figure 1). The reddish-white coloration and rubbery consistency of the lesion are non-specific but can be seen in various benign and malignant soft tissue tumors. The presence of ulceration further raises the suspicion of malignancy, as previously discussed. The solid white appearance of the cut surface suggests a dense cellular composition, and the lack of a clear capsule may indicate infiltrative growth, a feature often associated with malignancy. Imprint cytology, a technique involving the transfer of cells from the cut surface of the tissue onto a glass slide, was performed. Microscopic examination of the imprint smear revealed a cellular smear with an increased nuclear-to-cytoplasmic (N/C) ratio. The cells exhibited round-oval nuclei with uniform, hyperchromatic chromatin, and some nuclei appeared to be molding, forming a sheet-like structure. Some cells were bound to stromal fragments. The smear also showed a distribution of macrophages, lymphocyte cells, and polymorphonuclear (PMN) leukocytes (Figure 2). The cytological features observed in the imprint smear are concerning for malignancy. The increased N/C ratio is a characteristic of rapidly proliferating cells, often seen in malignant tumors. The hyperchromatic nuclei and nuclear molding further support this suspicion.

The presence of inflammatory cells, such as macrophages and lymphocytes, may reflect the host's immune response to the tumor. Intraoperative frozen section examination, a rapid diagnostic technique that allows for real-time assessment of tissue during surgery, was performed. The initial frozen section revealed skin tissue with a surface lined by stratified squamous keratinized epithelium, partially eroded. The underlying connective tissue stroma contained a proliferation of cells with hyperchromatic, angulated nuclei, some with visible nucleoli. These cells formed a cribriform structure containing basophilic mucus, with some forming solid sheets and tubular structures. The cells were observed infiltrating between the hyalinized connective tissue stroma to the striated muscle tissue, the intraepidermal layer, and around the nerve tissue. No lymphovascular tumor emboli were identified (Figure 3). The findings on the frozen section are consistent with a malignant salivary gland tumor, specifically adenoid cystic carcinoma (ACC). The presence of cribriform, solid, and tubular patterns is a hallmark of ACC. The infiltration of tumor cells into surrounding tissues, including muscle, epidermis, and nerve tissue, highlights the invasive nature of this malignancy. The perineural invasion observed further supports the diagnosis of ACC and raises concerns about the potential for local recurrence and distant metastasis. Based on the combined findings from the macroscopic examination, imprint cytology, and intraoperative frozen section analysis, a diagnosis of a malignant lesion was rendered. This intraoperative diagnosis is crucial for guiding surgical management. The identification of a malignant tumor with perineural invasion necessitates a wide local excision to ensure complete tumor removal with negative margins. The frozen section analysis allows for real-time assessment of the surgical margins, ensuring that all tumor tissue is removed and minimizing the risk of local recurrence. It is important to note that while the intraoperative frozen section diagnosis provides valuable information for immediate surgical decision-making, it is not a substitute for the definitive diagnosis obtained from permanent sections. The frozen section technique has limitations, including potential artifacts introduced by freezing and limited ability to perform special stains or immunohistochemical studies. Therefore, the final diagnosis is confirmed on histopathological examination of the paraffin-embedded tissue, which allows for more detailed evaluation and ancillary studies if needed (Table 2).

Following the intraoperative assessment, the excised tissue underwent routine processing and embedding in paraffin wax. This allowed for the preparation of thin tissue sections that were stained with hematoxylin and eosin (H&E) and examined under a light microscope. Microscopic examination of the H&E-stained sections confirmed the presence of skin tissue with a surface partially covered by stratified squamous keratinized epithelium, exhibiting areas of erosion. This corroborated the macroscopic observation of ulceration on the lesion's surface. Beneath the epithelium, the connective tissue stroma displayed a proliferation of basaloid cells with uniform, hyperchromatic nuclei, ranging in shape from angulated to oval. Some cells contained vesicular subnuclei, while others exhibited clear to eosinophilic cytoplasm. The basaloid appearance of the proliferating cells is a characteristic feature of several salivary gland tumors, including ACC. The hyperchromatic nuclei and variations in cytoplasmic staining reflect the cellular atypia associated with malignancy. The presence of vesicular subnuclei suggests active transcription and protein synthesis, further supporting the diagnosis of a neoplastic process. These cells were arranged in various architectural patterns, including cribriform structures containing basophilic mucus and eosinophilic hyaline material. Cribriform, meaning "sieve-like," describes the characteristic arrangement of tumor cells around acellular spaces. These spaces often contain extracellular matrix components, such as basement membrane material and glycosaminoglycans, which contribute to the basophilic staining observed in this case. The eosinophilic hyaline material may represent areas of collagen deposition or other extracellular

matrix proteins. In addition to the cribriform pattern, the tumor cells also formed solid sheets and tubular structures. The solid sheets were composed of densely packed basaloid cells with minimal intervening stroma. The tubular structures were lined by epithelial cells with round nuclei and eosinophilic cytoplasm, resembling ductal formations. This diversity in architectural patterns is a hallmark of ACC and reflects the tumor's ability to recapitulate various aspects of normal salivary gland architecture. Importantly, the tumor cells exhibited infiltrative growth, extending between the hyalinized and partially myxoid connective tissue stroma. They invaded the striated muscle tissue, the intraepidermal layer, and the perineural spaces. This infiltrative growth pattern is a key feature of ACC and contributes to its locally aggressive behavior. The invasion of surrounding structures, including muscle and nerves, highlights the tumor's potential to cause significant morbidity. Perineural invasion, the invasion of tumor cells into the spaces surrounding nerves, is a particularly concerning finding in ACC. It is associated with an increased risk of local recurrence, distant metastasis, and poor prognosis. The exact mechanisms underlying perineural invasion are not fully understood but are thought to involve complex interactions between tumor cells and the nerve microenvironment. No lymphovascular tumor cell emboli were identified in the examined sections. This suggests that the tumor had not yet spread through the lymphatic or blood vessels, indicating a lower risk of regional or distant metastasis at the time of diagnosis. Based on the comprehensive histopathological evaluation, a definitive diagnosis of adenoid cystic carcinoma was rendered. The presence of characteristic cribriform, solid, and tubular patterns, coupled with the infiltrative growth pattern and perineural invasion, confirmed the diagnosis. The absence of lymphovascular tumor emboli was also noted. The tumor was staged according to the TNM classification system, a widely used system for classifying the extent of cancer spread. In this case, the tumor was classified as pT3NxMx. This indicates that the tumor had invaded adjacent structures (T3), but the status of regional lymph nodes (N) and distant metastasis (M) could not be assessed based on the available information. The surgical margins were carefully examined and found to be free of tumors. This is a critical factor in predicting the likelihood of local recurrence. Achieving tumor-free margins is a primary goal of surgical resection for ACC and significantly improves the chances of long-term disease control (Table 3).

Following the intraoperative diagnosis of adenoid cystic carcinoma (ACC) and confirmation of tumor-free margins via frozen section analysis, a comprehensive treatment plan was implemented, focusing on surgical intervention and supportive care. The primary treatment modality for ACC is surgical resection with the goal of achieving complete tumor removal with negative margins. In this case, a wide local excision of the mass was performed. The extent of resection was guided by the intraoperative frozen section findings, which confirmed the presence of ACC and allowed for real-time assessment of the surgical margins. This approach ensures that all microscopically detectable tumor tissue is removed, minimizing the risk of local recurrence. In addition to surgical excision, the patient received intravenous fluid therapy with Tutofusin at a rate of 500 ml every 8 hours. Tutofusin is a balanced crystalloid solution used for fluid replacement and electrolyte balance maintenance. This is a standard practice in the perioperative period to maintain adequate hydration and hemodynamic stability. The patient was also administered a combination of medications for pain management, infection prophylaxis, and gastric protection. Ceftriaxone, a third-generation cephalosporin antibiotic, was prescribed at a dosage of 2 grams once daily for prophylaxis against surgical site infections. Ketorolac, a nonsteroidal anti-inflammatory drug (NSAID), was given at a dosage of 30 mg three times daily for pain control. Ranitidine, a histamine H2-receptor antagonist, was administered at a dosage of 50 mg twice daily to prevent stress-related ulcers and gastric complications. The patient's postoperative

recovery was closely monitored. He recovered well from the surgery and was discharged home on the third postoperative day. This relatively short hospital stay suggests that the surgery was well-tolerated and the patient experienced no significant postoperative complications. Regular follow-up examinations were scheduled to monitor for any signs of recurrence and assess the patient's overall health. At the 6-month follow-up visit, the patient remained disease-free. This is an encouraging finding, but it is essential to emphasize that ACC is known for its late recurrence, and long-term surveillance is crucial. The treatment and follow-up strategy employed in this case aligns with the current standard of care for ACC. Surgical resection remains the cornerstone of treatment, and achieving negative margins is paramount for maximizing local control and improving long-term outcomes. The use of intraoperative frozen section analysis is a valuable tool in guiding surgical resection and ensuring complete tumor removal. Adjuvant radiotherapy may be considered in cases with high-risk features, such as positive surgical margins, perineural invasion, or advanced T stage. However, the decision to administer adjuvant radiotherapy is individualized based on the patient's specific circumstances and risk factors. In this case, the patient had negative surgical margins and was closely monitored for any signs of recurrence. The use of systemic chemotherapy in the management of ACC is generally reserved for patients with unresectable or metastatic disease. It has shown limited efficacy in the adjuvant setting for localized disease. Therefore, chemotherapy was not indicated in this case. Long-term follow-up is essential for patients with ACC. Regular clinical examinations, imaging studies, and other investigations may be employed to detect recurrence early. The frequency and intensity of follow-up are tailored to the individual patient's risk factors and clinical course (Table 4).

Table 1. Anamnesis, clinical findings, imaging, and clinical diagnosis.

Anamnesis	Clinical findings	Imaging	Clinical diagnosis
44-year-old male. 2-year history of a slow-growing nodule on the upper lip; Occasional pain in the nodule. No facial numbness, paresthesia, fever, or weight loss. No history of similar illnesses or radiation therapy. Referred from another hospital with a suspected malignancy diagnosis	Nodule with slight ulceration on the upper lip. Nodule size: 3x2x1 cm. Firm consistency. Indistinct borders. Slight pain upon palpation. No palpable lymph nodes in the neck	No radiological abnormalities on chest radiography. No abnormalities in the thyroid or lymphadenopathy in the neck or preauricular regions on ultrasound	Malignancy of salivary gland

Table 2. Macroscopic, imprint, and intraoperative frozen section examination.

Macroscopic findings	Imprint cytology findings	Intraoperative frozen section findings	Diagnosis
Reddish-white, rubbery, solid skin tissue measuring 3x2x1.5 cm. Ulceration with a diameter of 0.5 cm on the skin surface. Solid white mass with a diameter of 2.5 cm, unclear capsule on cross-section (Figure 1).	Cellular smear with increased N/C ratio, round-oval nuclei, uniform, hyperchromatic, some nuclei appear molding, forming a sheet structure. Some cells are bound to stromal fragments. Distribution of macrophages and lymphocyte cells and PMN leukocytes (Figure 2).	Skin tissue with a surface lined by stratified squamous keratinized epithelium, partially eroded. Connective tissue stroma contains the proliferation of cells with hyperchromatic, angulated nuclei; some with visible nucleoli. Cells form a cribriform structure containing basophilic mucus, some forming solid sheets and tubular structures. Cells infiltrate between the hyalinized connective tissue stroma to the striated muscle tissue, the intraepidermal layer, and around the nerve tissue. No lymphovascular tumor emboli (Figure 3).	Malignant lesion

Table 3. Histopathological examination of the paraffin block.

Histopathological findings	Diagnosis
Skin tissue sections with surfaces covered with stratified squamous keratinized epithelium that is partly eroded. The underlying connective tissue stroma contains a proliferation of basaloid cells with uniform, angulated to oval, hyperchromatic nuclei; some with vesicular subnuclei; some with clear cytoplasm to eosinophilic. These cells form cribriform structures containing basophilic mucus and eosinophilic hyaline material. Some form solid sheets, and some form tubular structures covered with epithelial cells with round nuclei, and eosinophilic cytoplasm. These cells grow infiltratively between the hyalinized and partially myxoid connective tissue stroma to the striated muscle tissue and invade the intraepidermal layer and invade the perineural. No lymphovascular tumor cell emboli are seen (Figure 4).	Adenoid cystic carcinoma. Perineural invasion was found. No lymphovascular tumor cell emboli were seen. Minimal staging PT3NxMx. Tumor-free incision borders

Table 4. Treatment and follow-up.

Treatment	Follow up
Wide excision of the mass with tumor-free margins confirmed by intraoperative frozen section. IVFD tutofusin 500ml/8 hours. Injection ceftriaxone 2x1 gram. Injection ketorolac 3x30 mg. Injection of ranitidine 2x 50 mg.	The patient recovered well and was discharged home on the third postoperative day. The patient remains disease-free at 6 months postoperatively.

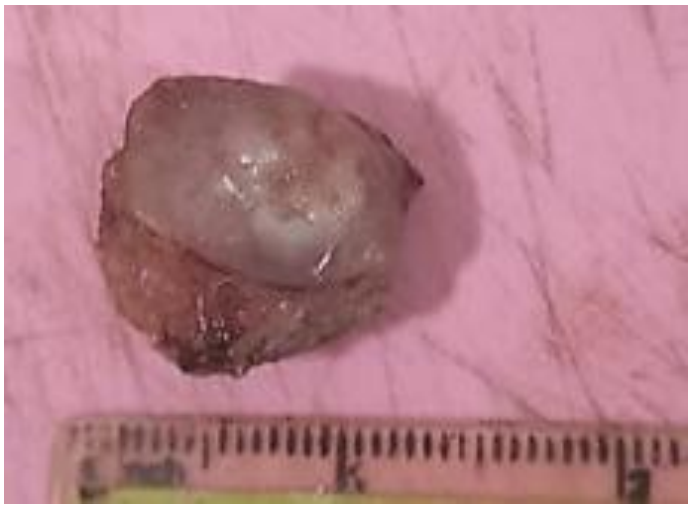

Figure 1. Macroscopic appearance of frozen section tissue.

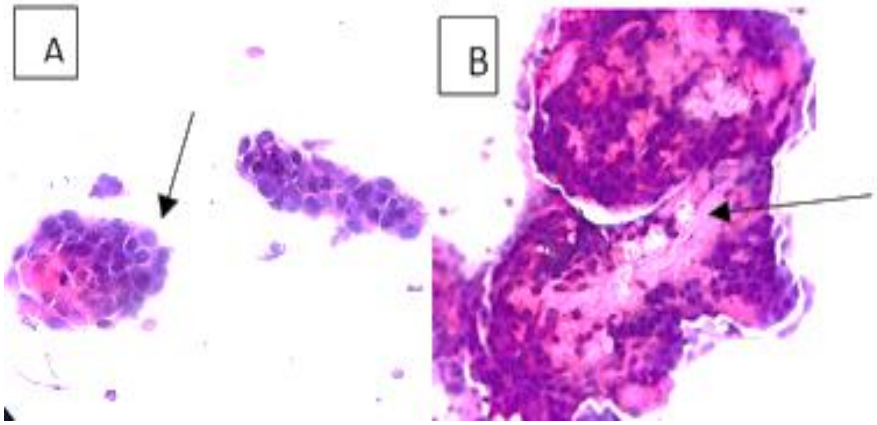

Figure 2. Microscopic examination of frozen section imprint cytology. (A) Cells with round to oval nuclei, uniform in size and shape, hyperchromatic (darkly stained), and exhibiting nuclear molding (where the nuclei are deformed due to close proximity to one another). These cells are arranged in sheets. (Hematoxylin and Eosin stain, 400x magnification). (B) Cells adhered to stromal fragments (fragments of the supporting connective tissue). (Hematoxylin and Eosin stain, 400x magnification).

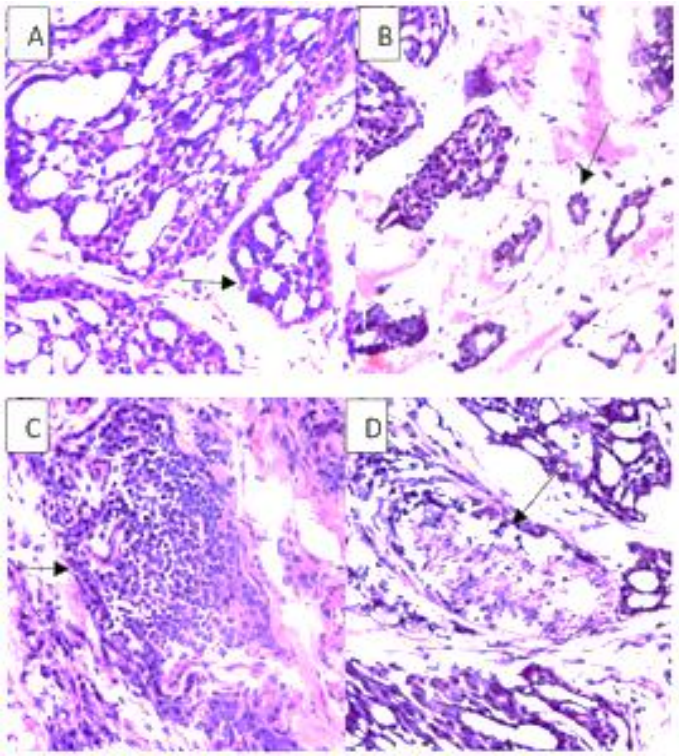

Figure 3. Microscopic appearance of frozen section of ACC. (A) Connective tissue stroma containing the proliferation of tumor cells forming a cribriform pattern. The cells have hyperchromatic, angulated nuclei, some with prominent nucleoli. The spaces contain basophilic mucus (H&E, 400x). (B) Tubular pattern (H&E, 400x). (C) Solid pattern (H&E, 400x). (D) Perineural invasion (H&E, 400x).

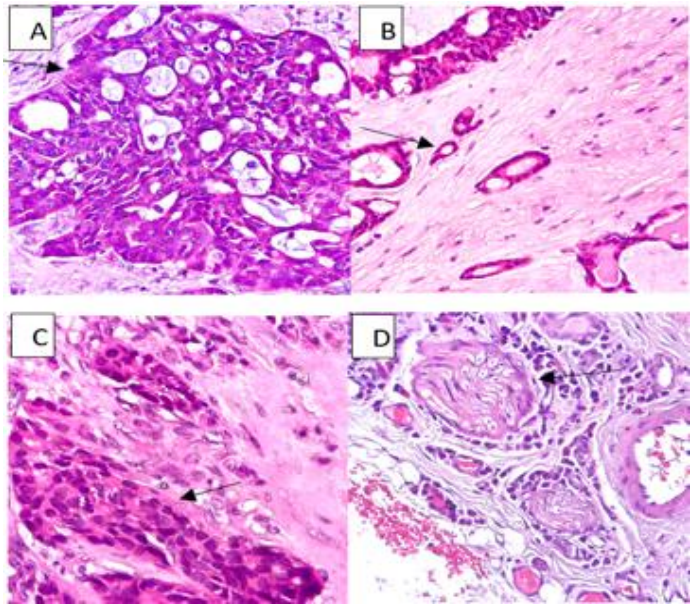

Figure 4. Microscopic appearance of ACC in paraffin block. (A) Connective tissue stroma containing a proliferation of basaloid cells forming cribriform structures. The cells have uniform, angulated to oval, hyperchromatic nuclei; some with vesicular subnuclei and some with prominent nucleoli. The cytoplasm ranges from scant to eosinophilic. The lumens contain basophilic mucus and eosinophilic hyaline material (H&E, 400x). (B) Tubular pattern lined by epithelial cells with round nuclei and eosinophilic cytoplasm. Some lumens contain basophilic mucus and eosinophilic hyaline material (H&E, 400x). (C) Solid pattern characterized by solid tumor nests lacking pseudocystic spaces (H&E, 400x). (D) Perineural invasion (H&E, 400x).

3. Discussion

Adenoid cystic carcinoma (ACC) is a rare malignancy that accounts for approximately 1% of all head and neck cancers and 10% of all salivary gland malignancies. It is characterized by its slow growth, but it is also known for its aggressive local invasion and high propensity for perineural invasion (PNI). PNI is a significant indicator of malignancy and is associated with an increased risk of local recurrence and distant metastasis. ACC most commonly arises in the major salivary glands, such as the parotid and submandibular glands, but it can also occur in the minor salivary glands. The most common site for ACC in the minor salivary glands is the palate, followed by the tongue, buccal mucosa, lips, and floor of the mouth. The diagnosis of ACC can be challenging, especially during intraoperative frozen section consultation. This is because ACC can have overlapping morphologic patterns and similar cell types with other benign and malignant salivary gland tumors. The distinction between ACC and these other entities can be difficult, particularly due to the limited sampling inherent to frozen sections. The use of frozen section diagnosis in the management of salivary gland tumors is well-established. It provides immediate information about the nature of the lesion, its margin status, and the presence of PNI, which can significantly influence surgical decision-making. This case report describes a case of ACC of the minor salivary gland diagnosed on frozen section, highlighting the importance of this technique in guiding surgical management and ensuring tumor-free margins, which are critical for patient prognosis. The clinical presentation of ACC is often nonspecific, contributing to delays in diagnosis and potential misdiagnosis. In the salivary glands, it typically manifests as a slow-growing, painless mass. However, as the tumor progresses, it can cause pain, facial nerve paralysis, or difficulty swallowing. In other sites, such as the sinonasal tract, symptoms may include

nasal obstruction, epistaxis, or proptosis. Due to its nonspecific presentation, ACC is often misdiagnosed or diagnosed at an advanced stage, highlighting the need for increased awareness and prompt diagnostic evaluation. The diagnosis of ACC requires a multi-pronged approach, encompassing clinical evaluation, imaging studies, and histopathological examination. Imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), are crucial for assessing the tumor's size, location, and extent of invasion. However, the definitive diagnosis rests on the histopathological examination of a biopsy specimen. The pathologist evaluates the cellular morphology, growth patterns, and presence of PNI to confirm the diagnosis. Intraoperative frozen section examination plays a pivotal role in the management of ACC. This rapid diagnostic technique provides real-time information about the nature of the lesion, its margin status, and the presence of PNI, allowing surgeons to make informed decisions during the operation. In the case presented, the frozen section diagnosis of ACC enabled the complete excision of the tumor with tumor-free margins, a critical factor in minimizing the risk of local recurrence and improving patient prognosis. The accuracy of frozen section diagnosis of salivary gland tumors has been reported to be high, with sensitivity and specificity rates of 90% and 99%, respectively. However, errors can occur, especially in the distinction between ACC and other salivary gland tumors with similar morphologic features. The treatment of ACC typically involves a multidisciplinary approach, with surgery being the mainstay of therapy. The goal of surgery is to achieve complete tumor removal with negative margins, minimizing the risk of local recurrence. However, due to the infiltrative nature of ACC and its propensity for PNI, achieving wide surgical margins can be challenging. In cases where complete resection is not feasible or when there is a high risk of recurrence, adjuvant radiotherapy is often recommended. Chemotherapy has a limited role in the treatment of ACC but may be considered in patients with advanced or metastatic disease. The prognosis of ACC is variable and depends on several factors, including the tumor's location, stage, histologic grade, and presence of PNI. Despite advances in treatment, ACC is known for its late recurrence and propensity for distant metastasis. Long-term follow-up is essential to monitor for recurrence and manage potential complications. Given the propensity of ACC for late recurrence, long-term surveillance is paramount. Regular follow-up examinations, including clinical assessments and imaging studies, are crucial for detecting recurrence early and initiating prompt intervention. The frequency and intensity of follow-up are tailored to the individual patient's risk factors and clinical course.[11-13]

Adenoid cystic carcinoma (ACC) is notorious for its varied and often subtle clinical presentations, making early diagnosis a significant challenge. Understanding the diverse manifestations of this disease is crucial for clinicians to ensure timely intervention and appropriate management. The clinical presentation of ACC can vary significantly depending on the tumor's location, size, and growth pattern. However, some common features can aid in raising suspicion for this malignancy. In the major and minor salivary glands, ACC typically presents as a slow-growing, painless mass. The lack of pain in the early stages often contributes to delayed diagnosis as patients may not seek medical attention until the tumor has reached a considerable size. As the tumor progresses, it can cause pain, facial nerve paralysis (if the tumor involves the facial nerve), or difficulty swallowing (if the tumor obstructs the pharynx or esophagus). When ACC arises in the sinonasal tract, it may cause nasal obstruction, epistaxis (nosebleeds), or proptosis (bulging of the eye) if the tumor extends into the orbit. The nonspecific nature of these symptoms can lead to misdiagnosis as sinusitis or other benign conditions. ACC can also occur in other locations where minor salivary glands are present, such as the trachea, bronchi, lacrimal glands, and breast. The symptoms in these cases will depend on the specific site of origin and the extent of tumor involvement. The diagnosis of ACC presents several challenges due to its varied

clinical presentation, overlapping features with other salivary gland tumors, and the need for specialized diagnostic techniques. The initial symptoms of ACC are often nonspecific and can mimic those of benign conditions, leading to delays in diagnosis. Patients may attribute their symptoms to other causes, and clinicians may not immediately suspect ACC, especially in its early stages. ACC can exhibit a variety of histologic patterns that overlap with other salivary gland tumors, both benign and malignant. This can make it challenging to distinguish ACC from other entities based on histologic features alone. The propensity of ACC for perineural invasion (PNI) adds another layer of complexity to diagnosis. PNI may not be readily apparent on clinical examination or imaging studies, and specialized histologic techniques may be required to identify it. The definitive diagnosis of ACC requires a biopsy, which can be obtained through fine-needle aspiration cytology (FNAC) or an incisional or excisional biopsy. The choice of biopsy technique depends on the tumor's location, size, and accessibility. To overcome the diagnostic challenges posed by ACC, a multi-pronged approach is essential, combining clinical suspicion, appropriate imaging studies, and expert histopathological evaluation. A high index of suspicion is crucial for early diagnosis. Clinicians should consider ACC in the differential diagnosis of any slow-growing mass in the salivary glands or other sites where minor salivary glands are present. A thorough history and physical examination, including a cranial nerve assessment, are essential. Imaging studies, such as computed tomography (CT) and magnetic resonance imaging (MRI), play a vital role in evaluating the tumor's size, location, and extent of invasion. These studies can also help identify PNI, although it may not always be readily apparent on imaging. The cornerstone of ACC diagnosis is histopathological examination. A biopsy specimen should be carefully evaluated by an experienced pathologist to assess the cellular morphology, growth patterns, and presence of PNI. Immunohistochemical stains may be used to aid in the diagnosis and differentiate ACC from other salivary gland tumors. A multidisciplinary approach involving clinicians from various specialties, including otolaryngology, pathology, radiology, and oncology, is often necessary for optimal diagnosis and management of ACC.[14-16]

Intraoperative frozen section examination plays a pivotal role in the management of adenoid cystic carcinoma (ACC). This rapid diagnostic technique provides real-time information about the nature of the lesion, its margin status, and the presence of perineural invasion (PNI), allowing surgeons to make informed decisions during the operation. In the case presented, the frozen section diagnosis of ACC enabled the complete excision of the tumor with tumor-free margins, a critical factor in minimizing the risk of local recurrence and improving patient prognosis. The accuracy of frozen section diagnosis of salivary gland tumors has been reported to be high, with sensitivity and specificity rates of 90% and 99%, respectively. However, errors can occur, especially in the distinction between ACC and other salivary gland tumors with similar morphologic features. Frozen section diagnosis provides immediate information about the nature of the lesion, allowing surgeons to make informed decisions during the operation. This is particularly important in cases of ACC, where the extent of resection can be tailored based on the presence of PNI or positive margins. Frozen section analysis allows for real-time assessment of surgical margins, ensuring that all tumor tissue is removed and minimizing the risk of local recurrence. In cases where wide resection is necessary, frozen section diagnosis can guide the planning of reconstructive procedures. By providing immediate information about margin status, frozen section diagnosis can reduce the need for a second surgery to achieve clear margins. The freezing process can introduce artifacts that may obscure some histologic details, potentially affecting diagnostic accuracy. Frozen sections typically represent only a small portion of the tumor, potentially missing areas of PNI or other important diagnostic features. Frozen section diagnosis requires specialized training and expertise. The accuracy of the diagnosis depends on the skill and experience of the

pathologist performing the interpretation. The accuracy of frozen section diagnosis of salivary gland tumors has been reported to be high, with sensitivity and specificity rates of 90% and 99%, respectively. However, errors can occur, especially in the distinction between ACC and other salivary gland tumors with similar morphologic features. In the case presented, the frozen section diagnosis of ACC was concordant with the final histopathological diagnosis. This highlights the effectiveness of frozen section diagnosis in guiding surgical management of salivary gland tumors, even in cases with complex morphology.[17,18]

The management of adenoid cystic carcinoma (ACC) often requires a multidisciplinary approach, with treatment strategies tailored to the individual patient's needs and disease characteristics. The primary goals of treatment are to achieve local control, minimize the risk of recurrence, and preserve quality of life. Surgery is the cornerstone of treatment for ACC. The goal of surgery is to achieve complete tumor removal with negative margins, minimizing the risk of local recurrence. However, due to the infiltrative nature of ACC and its propensity for perineural invasion (PNI), achieving wide surgical margins can be challenging. The extent of surgery depends on factors such as tumor location, size, and the presence of PNI. Adjuvant radiotherapy is often recommended in cases where complete resection is not feasible or when there is a high risk of recurrence. Radiotherapy can help to destroy any residual tumor cells and reduce the risk of local recurrence. Chemotherapy has a limited role in the treatment of ACC but may be considered in patients with advanced or metastatic disease. It may also be used in neoadjuvant or adjuvant settings in certain cases. Targeted therapies are drugs that specifically target molecules involved in cancer cell growth and survival. Some targeted therapies have shown promise in the treatment of ACC, particularly those targeting the epidermal growth factor receptor (EGFR). Immunotherapy is a type of treatment that harnesses the body's immune system to fight cancer. Some immunotherapy drugs, such as checkpoint inhibitors, have shown encouraging results in clinical trials for ACC. The stage of the tumor, which reflects its size and extent of spread, is a significant prognostic factor. Early-stage tumors have a better prognosis than advanced-stage tumors. The grade of the tumor, which reflects how abnormal the cancer cells look under a microscope, can also affect prognosis. High-grade tumors tend to grow and spread more quickly than low-grade tumors. The presence of PNI is a strong predictor of poor prognosis. PNI is associated with an increased risk of local recurrence, distant metastasis, and decreased survival. Achieving negative surgical margins is crucial for minimizing the risk of local recurrence and improving long-term outcomes. The patient's overall health and comorbidities can also influence prognosis. Long-term follow-up is essential for patients with ACC. Regular follow-up examinations, including clinical assessments and imaging studies, are crucial for detecting recurrence early and initiating prompt intervention. The frequency and intensity of follow-up are tailored to the individual patient's risk factors and clinical course.[19,20]

4. Conclusion

This case report presents a rare case of adenoid cystic carcinoma (ACC) arising in the minor salivary gland of the upper lip, diagnosed definitively through intraoperative frozen section examination. The patient's clinical presentation, a slow-growing nodule with occasional pain, aligned with the typical characteristics of ACC. The absence of neurological symptoms and systemic signs further contributed to the clinical picture. Imaging findings, including normal chest radiography and an absence of thyroid or lymph node abnormalities on ultrasound, indicated localized disease. However, the definitive diagnosis was achieved through histopathological examination. Macroscopic examination of the excised tissue revealed a reddish-white, rubbery, solid mass with ulceration, suggestive of malignancy. Imprint cytology further supported this suspicion, showing cellular features indicative of malignancy. Intraoperative

frozen section examination confirmed the diagnosis of ACC, demonstrating the characteristic cribriform, solid, and tubular patterns of this malignancy. The identification of perineural invasion further underscored the diagnosis and guided the surgical management. Following the intraoperative diagnosis, wide local excision of the mass was performed to ensure complete tumor removal with negative margins. The patient's postoperative recovery was uneventful, and he remained disease-free at the 6-month follow-up. This case underscores the crucial role of intraoperative frozen section diagnosis in the management of ACC of the minor salivary glands. The accurate assessment of the lesion and margin status during surgery allows for appropriate surgical decision-making, ensuring complete tumor removal and minimizing the risk of recurrence. The findings emphasize the importance of a comprehensive diagnostic approach, incorporating clinical evaluation, imaging studies, and histopathological examination, in the diagnosis and management of ACC. The case also highlights the indolent nature of ACC and the necessity for long-term surveillance to monitor for recurrence and manage potential complications.

5. References

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