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Case Report

Carcinoma Ex Pleomorphic Adenoma - Report of a Rare Case in the Cheek Mucosa

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Abstract: Carcinoma ex pleomorphic adenoma (CEPA) is a malignization of pleomorphic adenoma and often evolves silently. Its occurrence is rare and predominantly affects the major salivary glands, with the palate being the most common intraoral location. It is recognized as a condition with difficult clinical and pathological diagnosis, and histopathology remains the gold standard for definitive diagnosis. This study presents a primary CEPA in the buccal mucosa identified in a 69-year-old female patient. Less invasive tumors are associated with good prognosis; therefore, early recognition is important as they can become more aggressive, leading to more comprehensive therapies and reserved prognoses.

Keywords: Pleomorphic adenoma; Carcinoma ex pleomorphic adenoma; Minor salivary glands.

1. Introduction

Pleomorphic adenoma (PA) is a benign neoplasm of epithelial origin that represents, on average, 3% of head and neck tumors and 80% of salivary gland tumors. It occurs more frequently in the parotid gland, followed by the submandibular gland and minor salivary glands. Usually, it is well-circumscribed, slow-growing, painless, and firm to the touch, with or without encapsulation. The longer the PA persists, the higher the likelihood of malignization, leading to three subtypes of malignant mixed tumors: carcinosarcoma, metastasizing pleomorphic adenoma, and carcinoma ex pleomorphic adenoma (CEPA). Approximately 1% to 7% of PAs transform into CEPA.

CEPA is a rare malignant tumor, estimated to occur in 0.17 tumors per 1 million people per year, representing about 3% to 5% of all salivary gland neoplasms and 5% to 15% of malignant tumors of these glands. It predominantly affects the major salivary glands, with most cases observed in the parotid and submandibular glands. It rarely arises in minor salivary glands, and when located in the oral cavity, the palate is the most commonly affected site.

Diagnostic methods may include fine-needle aspiration biopsy (FNAB) and cytology, ultrasonography, computed tomography, and magnetic resonance imaging. FNABs are widely used for diagnosing salivary gland tumors and are considered easy, inexpensive, quick to perform, and well-accepted by patients. However, cytology from FNABs has low

sensitivity in diagnosing CEPA. Currently, surgery is the primary treatment for CEPA. The extent of surgery should be individualized, and depending on the tumor's location, extent, and histological type, dissection of local lymph nodes and radiotherapy may be necessary.

Carcinoma ex pleomorphic adenoma of minor salivary glands is reported in the literature as a low-incidence entity and is predominantly located in the palate. Therefore, we aim to report a primary CEPA in the buccal mucosa near the upper right vestibular sulcus in a 69-year-old female patient.

2. Case Report

A 69-year-old female patient with leukoderma presented to the Stomatology Clinic in December 2019 with a complaint of increased volume in the inner region of the right cheek observed in the previous month. During anamnesis, the patient reported that the alteration was asymptomatic but was slowly increasing in size. Her past medical history included hypertension without other comorbidities. When asked about the use of chronic medications, past health issues, and family medical history, no response was relevant.

Extraoral physical examination did not reveal facial asymmetry, and lymph node palpation was negative. Intraoral examination showed edentulous arches with complete dentures. Oroscopy revealed an endophytic nodular lesion of rigid consistency, asymptomatic, located in the buccal mucosa near the posterior region of the right maxilla, measuring approximately 2 cm in its greatest diameter. The mucosa appeared intact, with normal coloration, and a slight increase in vascularity was noted on its surface (Figure 1). Panoramic radiography did not show relevant findings for the lesion (Figure 2), and fine-needle aspiration biopsy was negative.

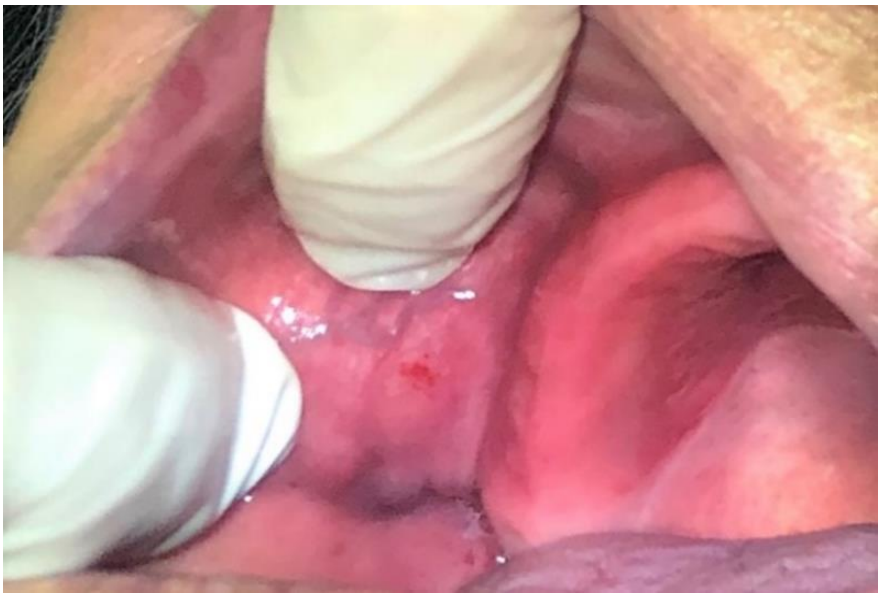

Figure 1: Clinical presentation of the lesion.

After the clinical examination, pleomorphic adenoma was considered the main diagnostic hypothesis. Due to the clinical characteristics suggestive of benignity, an excisional biopsy was performed under local anesthesia (Figure 3). Macroscopically, the lesion was encapsulated, measuring approximately 1.3 cm in diameter (Figure 4). The entire removed material was immersed in a 10% formalin solution and sent to the pathology laboratory.

Histopathological analysis revealed an adenomatous neoplasm with islands and cords of epithelial cells in a loose connective tissue stroma (pleomorphic adenoma) associated with lymphoid aggregates. The architectural alteration due to the presence of an encapsulated adenomatous structure was noted, within which neoplastic infiltration with

glandular/ductal structuring and a solid area with up to one mitosis per mm² were observed. The neoplasm infiltrating the capsule showed fibroplasia and mononuclear infiltrate. However, no extracapsular extension was evident, leading to the final diagnosis of intracapsular/minimally invasive carcinoma ex pleomorphic adenoma (Figures 5, 6, 7, and 8).

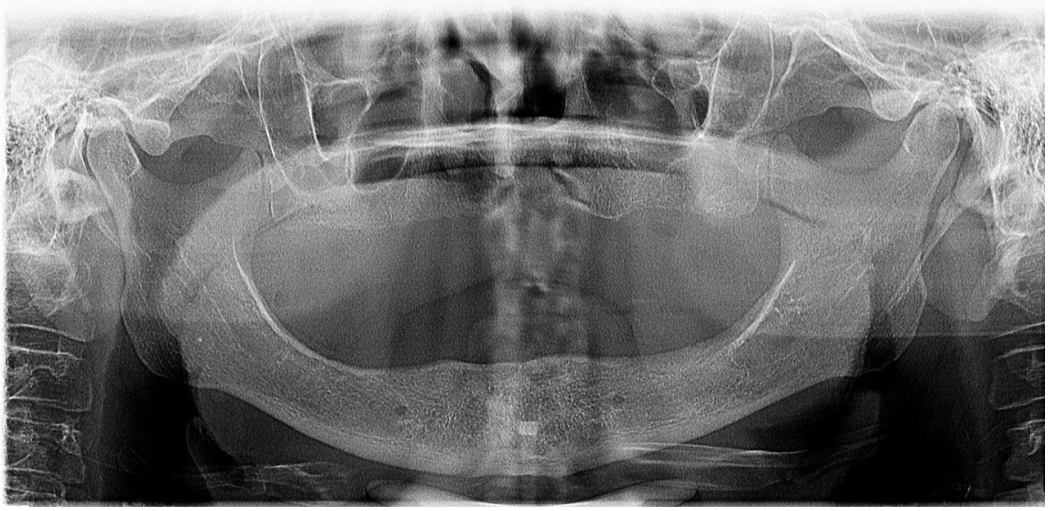

Figure 2: Panoramic radiograph without findings relevant to injury.

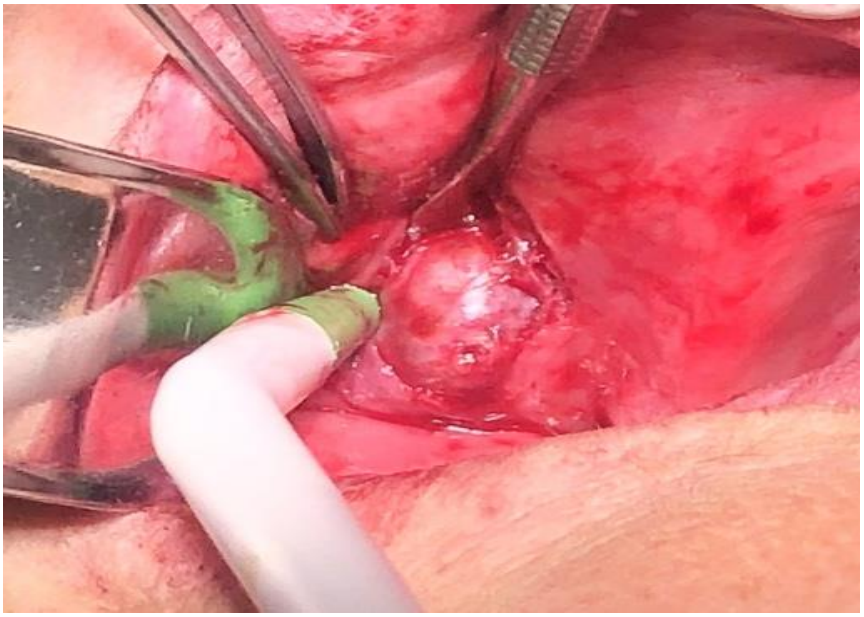

Figure 3: Transsurgical excisional biopsy.

Immunohistochemistry was requested for complementary evaluation, showing positive reactions for cytokeratin 7 (clone OV-TL 12/30), p53 protein (clone DO-7), and Ki-67 (clone MIB-1) in 15% of neoplastic cells, confirming the diagnosis of CEPA (Figures 9, 10, and 11). After the diagnosis, the patient was referred to the Oncology and Head and Neck Surgery Service for evaluation and treatment. The patient underwent surgical treatment and has been followed up for 12 months.

3. Discussion

CEPA is an uncommon entity with distinct clinical and pathological relevance. It has a low incidence in minor salivary glands, with the palate being the most commonly

affected intraoral site. To date, there are few reports of this tumor in the intraoral region published in the specialized literature.

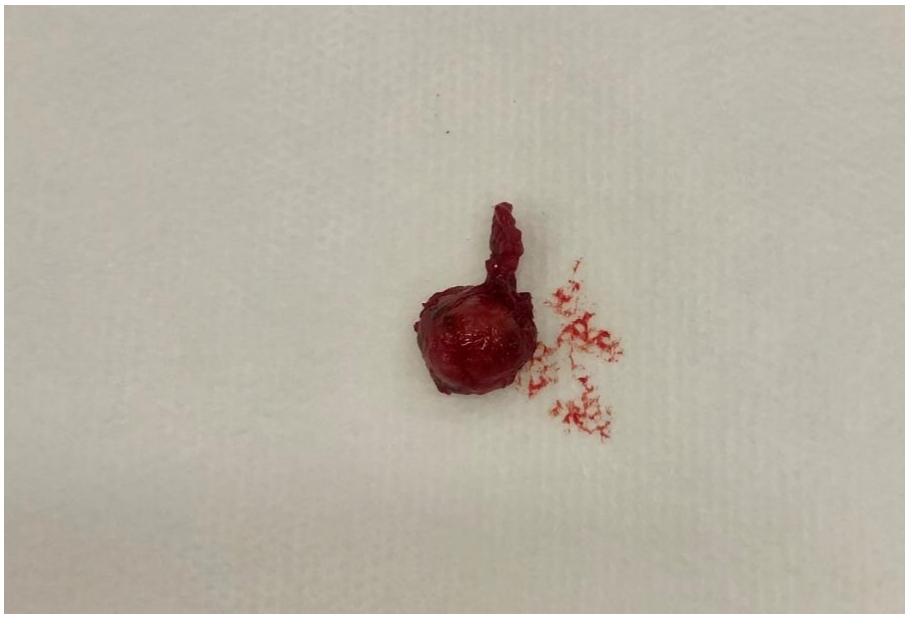

Figure 4: Lesion removed, sent for histopathological examination.

Among the 151 CEPA cases retrospectively reviewed from 1960 to 2015 by Ye et al., 50.3% affected the parotid gland, and only 13 lesions (8.6%) were located in minor salivary glands, found in the floor of the mouth, lip, and tongue. Seok et al. conducted a recent study comparing the clinical characteristics between carcinoma ex pleomorphic adenoma and pleomorphic adenoma. They analyzed 236 patient records from a single hospital between 2008 and 2017, including 221 patients with pleomorphic adenoma and 15 cases of CEPA. The CEPA cases were distributed as follows: 60% in the parotid gland, 20% in the submandibular gland, and 13.3% in minor salivary glands in the tongue and palate. Unlike most cases described in the literature, the present case describes a rare primary CEPA in the buccal mucosa.

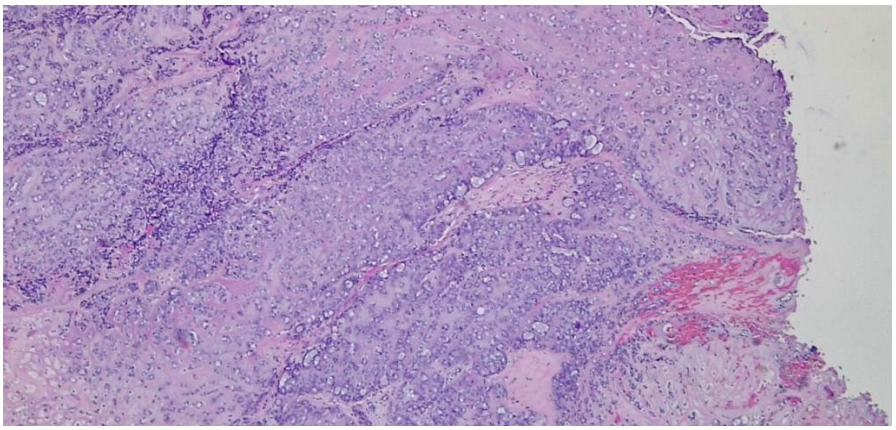

Figure 5: Carcinoma ex-intracapsular/minimally invasive pleomorphic adenoma – area of pleomorphic adenoma without atypia. HE 40X.

CEPA has a higher incidence in middle-aged patients, with a prevalence between the 5th and 7th decades of life. However, isolated cases have been reported in young patients,

such as the case presented by Kini et al. of a tumor located in the buccal mucosa in a 17-year-old patient. The patient's age, 69 years, is in line with the literature regarding the higher incidence of CEPA. Signs and symptoms associated with the malignant transformation of pleomorphic adenoma include rapid growth, changes in consistency, pain, facial nerve paresthesia, superficial vascular alterations, and necrosis. In the present case, most of these characteristics were not evident, but a slight increase in vascularity was noted on the lesion's surface. These signs and symptoms were also absent in the case studies presented by Kini et al. and Peter et al., demonstrating the clinical variability that these tumors can exhibit.

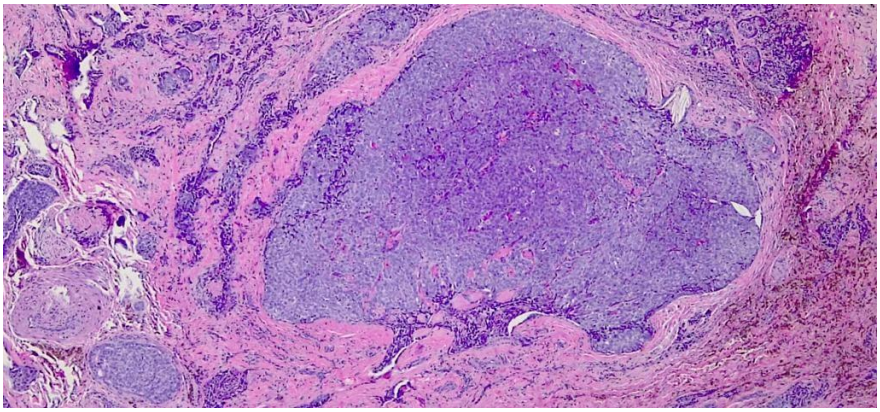

Figure 6: Area of intracapsular carcinoma.

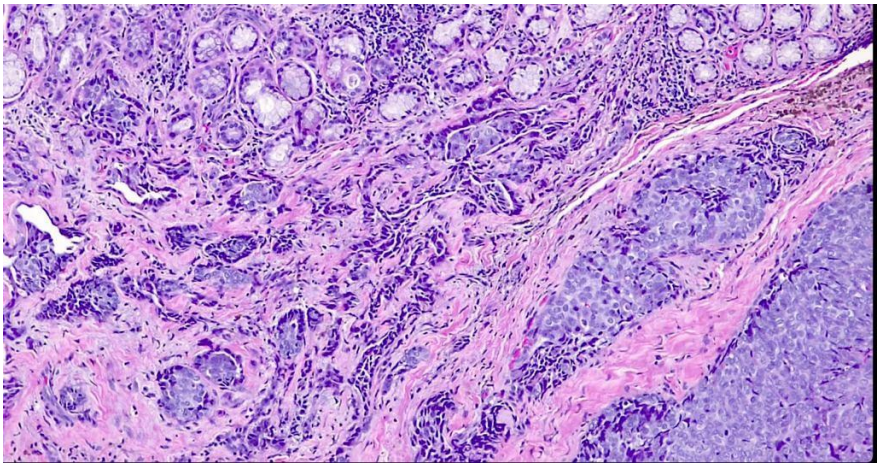

Figure 7: Detail of the minimally invasive focus towards the minor mucosal salivary gland. HE 100x zoom.

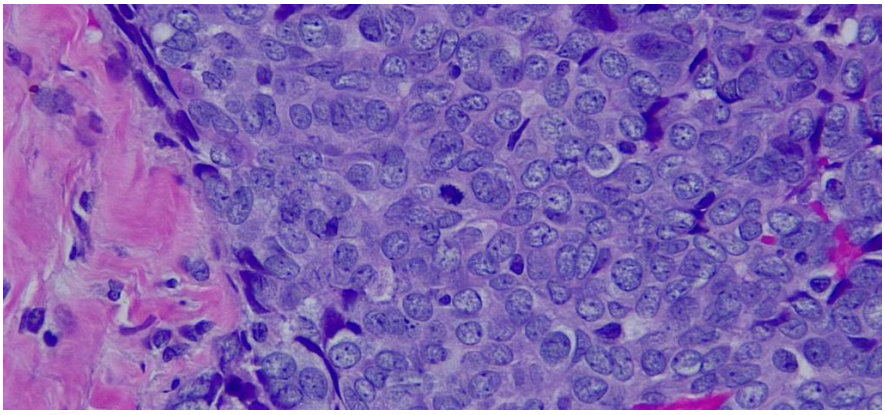

Figure 8: Mitosis 400x.

The pleomorphic adenoma is a glandular tumor of salivary origin, commonly found in major salivary glands, such as the parotids, and is known for its benign nature. The development time, size, and recurrence of these pleomorphic adenomas can vary from patient to patient. However, typically, these adenomas grow slowly over the years and can reach considerable sizes before being noticed. Among these characteristics, some may contribute to the transformation into Carcinoma Ex-Pleomorphic Adenoma:

- Duration and Tumor Growth: The duration of pleomorphic adenoma can be a contributing factor to malignant transformation. Adenomas of long duration have an increased potential to develop genetic alterations favoring malignancy.
- Adenoma Size: Larger pleomorphic adenomas may be associated with an increased risk of malignant transformation. Large tumors may undergo ischemic changes and necrosis, creating a conducive environment for malignant changes.
- Recurrence: Recurrent pleomorphic adenomas may have a higher potential for malignant transformation. Each recurrence can increase the probability of cumulative genetic alterations.

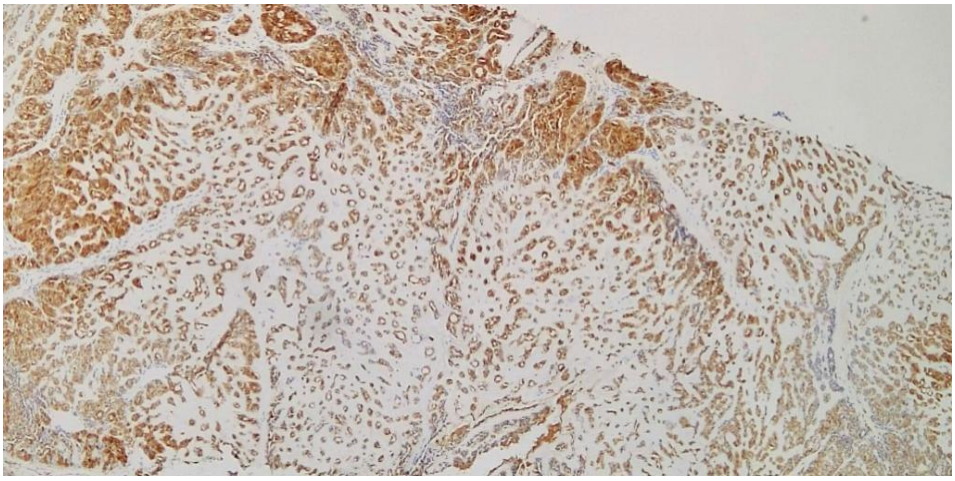

Figure 9: S100 – myoepithelial cells – pleomorphic adenoma area.

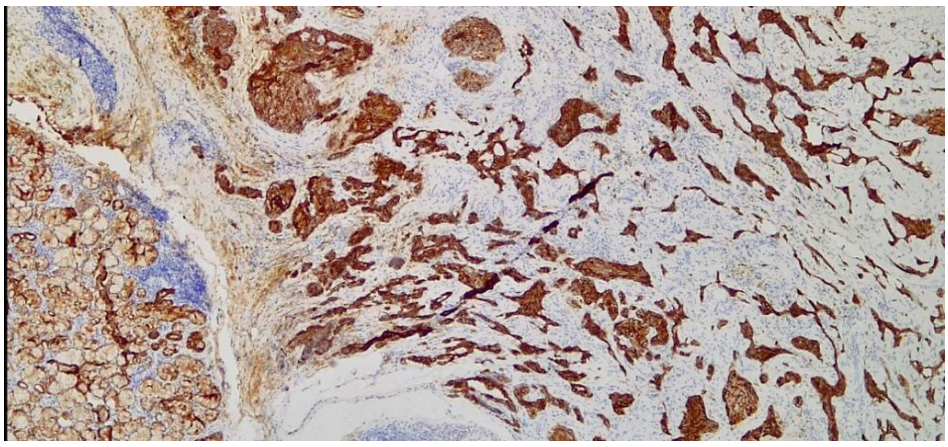

Figure 10: CK7 positive area of carcinoma invasion.

However, what draws attention in the reported case is that none of these factors were present in our patient. Numerous studies have been conducted to investigate the molecular and genetic alterations associated with the malignant transformation of pleomorphic adenoma. 1) Alterations in chromosome 8q have been observed in ex-pleomorphic

adenoma carcinomas. Deletions or amplifications in this region may contribute to progression to malignancy; 2) Mutations in tumor suppressor genes, such as p53 and p16, are frequently associated with malignant transformation. These mutations can lead to loss of cell cycle control and uncontrolled cell proliferation; 3) Chromosomal rearrangements, such as translocations and fusions, can also play a role in carcinogenesis by altering the expression of key genes and promoting progression to carcinoma; 4) Increased expression of cancer-associated molecular markers, such as Ki-67, can be observed in the malignant transformation of pleomorphic adenoma.

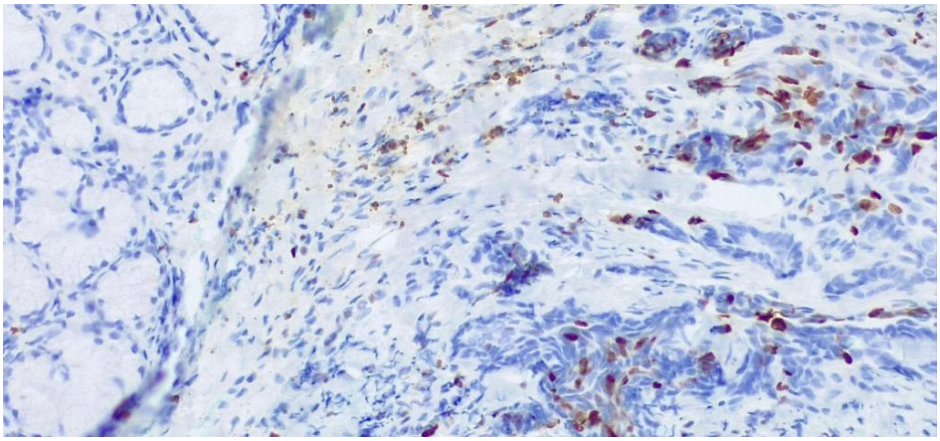

Figure 11: Ki67 in the adenoma area – positive in sparse cells.

It is recommended to avoid making definitive diagnoses based on small biopsy samples, as evaluating the entire lesion may be necessary to distinguish low-grade malignant tumors from pleomorphic adenoma. The histopathological distinction between high-grade CEPA, low-grade CEPA, and pleomorphic adenoma is crucial since treatment and prognosis differ for each of these neoplasms. The present clinical approach, based on the diagnostic hypothesis of Pleomorphic Adenoma, led to the choice of excisional biopsy of the lesion, and the entire removed material was sent for histopathological examination.

The diagnosis of CEPA requires the presence of residual pleomorphic adenoma and its malignant component. The most prevalent malignant components are adenocarcinoma, salivary duct carcinoma, myoepithelial carcinoma, and undifferentiated carcinoma. Other tumors have also been reported, such as mucoepidermoid carcinoma, acinic cell carcinoma, adenoid cystic carcinoma, and sarcomatoid carcinoma. The histopathological examination of the tumor described here identified an adenomatous neoplasm and an intracapsular/minimally invasive CEPA, with pathological staging pT1, and the immunohistochemical analysis detected the malignant component.

Patients with high-grade malignant components have a worse prognosis compared to patients with low-grade malignant components. Prognosis also depends on pathological staging parameters, such as invasion level, lymph node involvement, and the presence of metastases. In general, non-invasive CEPA cases have been associated with a favorable prognosis. Ye et al. concluded that frankly invasive CEPA is a high-grade neoplasm with an unfavorable prognosis, as 44.4% of patients in their study sample died from this disease. Even in cases of non-invasive and minimally invasive tumors, systematic follow-up after primary treatment is recommended, as three out of sixteen patients with such diagnoses developed metastases and two died. Additionally, tumor size is considered an important prognostic indicator. CEPA located in the buccal mucosa tends to be smaller than those occurring in major salivary glands.

The treatment options depend on the extent of the lesion. These can range from surgery, radiotherapy, chemotherapy, to molecular targeted therapy, each with advantages and disadvantages. In the case of the first option, if the surgery is successful and the tumor

is completely removed, the chances of a cure can be significant. The extent of the surgery can influence the quality-of-life post-treatment. On the other hand, the choice of Adjuvant Radiotherapy and Chemotherapy can improve local disease control and reduce recurrence rates. However, side effects must be considered.

Literature reviews reach a consensus on the importance of accurate diagnosis to determine surgical approach and adjuvant treatments, including radiotherapy, when necessary. For most lesions, surgery is the primary treatment for CEPA, and the surgical extent should be based on the tumor's size, location, and involvement of adjacent structures. In Ye et al.'s review, 64.2% of patients underwent only surgery, and 33.8% received adjuvant treatment with radiotherapy. Most cases treated with surgery and radiotherapy had lower rates of local recurrence compared to cases treated solely with surgery. They also reported that, for T1 and T2 tumors, the difference was not significant.

4. Conclusion

Based on this, we can conclude that carcinoma ex-pleomorphic adenoma in the buccal mucosa is a complex phenomenon influenced by temporal factors, tumor size, and adenoma recurrence, in addition to molecular and genetic alterations. Understanding these aspects is crucial for diagnosis, prognosis, and the development of effective therapeutic strategies. However, it is important to note that research in this area is constantly evolving, and it is recommended to consult updated sources for the latest information on the subject.

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Research Ethics Committee Approval: We declare that the patient approved the study by signing an informed consent form and the study followed the ethical guidelines established by the Declaration of Helsinki.

Acknowledgments: None.

Conflicts of Interest: None.

Supplementary Materials: None.

References

1. Ye P, Gao Y, Mao YC, Guo CB, Yu GY, Peng X. Carcinoma ex Pleomorphic adenoma: is it a high-grade malignancy. J Oral Maxillofac Surg, 2016; V:1-12.
2. Venegas O, Jaramillo L, Nicola M, Covarrubias N, Martínez B, Olivos B. Pleomorphic adenoma of the palate: Two cases report and literature review. J Oral Res 2014; 3(1): 46-49.
3. Rodrigues TF, Paula HM, Pereira CM. Relato de Caso, Adenoma Pleomórfico de glândula salivar menor. Revista Ciências e Odontologia, 2018; 2(2)1-4.
4. Weissferdt A, Langman G. An intracapsular carcinoma ex pleomorphic adenoma with lung metastases composed exclusively of benign elements: Histological evidence of a continuum between metastasizing pleomorphic adenoma and carcinoma ex pleomorphic adenoma. Pathology-Reserarch and Practice, 2010; 206, 408-483.Doi: 10.1016/j.prp.2009.07.008
5. Seok J, Hyun SJ, Jeong WJ, Ahn SH, Kim H, Jung HY. The Difference in the Clinical Features Between Carcinoma ex Pleomorphic Adenoma and Pleomorphic Adenoma. Ear, Nose & Throat Journal, 2019, V. 98(8) 504-509. Doi: 10.1177/0145561319855376
6. Carneiro DS, junior JCX, Gasparetto PF, Silva MAG, Pereira CM. Carcinoma ex pleomorfhic adenoma of the buccal region in a 53-yaer-old man patient. JOHS, 2011; 3(3)61-68. Doi: 10.5602/2229-3624.89.
7. Singh K, Agarwal C, Pujani M, Verma P, Chauhan V. Carcinoma Ex Pleomorphic Adenoma: A Diagnostic Challenge on Cytology. Wiley Periodicals, Inc. Diagnostic Cytopathology, 2017; 00:000-000. Doi: 10.1002/dc.
8. Antony J, Gopalan V, Smith RA, Lam AKY. Carcinoma ex Pleomorphic Adenoma: A Comprehensive Review of Clinical, Pathological and Molecular Data. Head and Neck Pathol, 2012; 6:1–9. Doi: 10.1007/s12105-011-0281-z.
9. Goyal P, Sehgal S, Ghosh S, Agrawal D, Singh S. Rare carcinoma ex-pleomorphic adenoma of buccal mucosa: case report and review of literature. Rare Tumors, 2016; V. 8:6138. Doi:10.408I/rt.2016.6138.
10. Kaneco H, Muramatsu T, Onozawa K, Yano H, Owada M, Abe H. Carcinoma ex Pleomorphic Adenoma Including Two Carcinoma Components Arising in the Palate. Kor J Oral Maxillofac Pathol 2012; 36(2):109-112.
11. Kini Y, Desai C, Mahindra U, Kalburge J. Rare carcinoma ex pleomorphic adenoma of the buccal minor salivary gland causing a therapeutic dilema. Contemporary Clinical Dentistry, 2012; V.3(2): 209-211. Doi: 10.41103/0976-237x.96832.

12. Zhao et al. Prognostic factors affecting the clinical outcome of carcinoma ex pleomorphic adenoma in the major salivar gland. World Journal of Surgical Oncology, 2013;11:180.
13. Yamamoto et al. A case of carcinoma ex pleomorphic adenoma arising from multinodular pleomorphic adenoma of the buccal region. Wileyonlinelibrary.com/jornal/cc3, 2019;7:1994-1998. Doi: 10.1002/ccr3.2417.
14. Reichart PA, Kalz S, Rabel A, Bornstein MM. Carcinoma ex pleomorphic adenoma in a minor salivar gland: report of a case. Oral Maxillfac Surg, 2010; 14:59-62. Doi: 10.1007/s10006-009-0183-3.
15. Okano K, Ishida M, Sandoh K, Fujisawa T, Iwai H, Tsuta K. Cytological features of carcinoma ex pleomorphic adenoma of the salivary glands: A diagnostic challenge. Diagnostic Cytopathology, 2019; 1-5. DOI: 10.1002/dc.24333.
16. Convinsky M, Cai Z, Ambelil M, Liu J, Zhu H. Low Grade Carcinoma Ex-Pleomorphic Adenoma: Diagnosis and Diagnostic Challenges Caused by Fine Needle Aspiration: Report of Three Cases and Review of Literature. Head and Neck Pathol, 2018; 12:82–88. Doi: 10.1007/s12105-017-0829-7.
17. Mok Y, Ming LC, Petersson F. Minimally invasive carcinosarcoma ex pleomorphic adenoma: A case report and literature review with cytohistological correlation. Wiley Online Library (wileyonlinelibrary.com), 2016. Doi: 10.1002/hed.24462.