International Clinical and Medical Case Reports Journal
Case Report (ISSN: 2832-5788)

Cribriform Adenocarcinoma of Minor Salivary Glands: A Rare Case Report with Diagnostic Challenges

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Citation: *Taha yassine Aaboudech, Hafsa El Ouazzani, Habiba Kadiri, Ayoub Bouteyine, Hanae Benadbdenbi, Naji Rguieg, et al. Cribriform Adenocarcinoma of Minor Salivary Glands: A Rare Case Report with Diagnostic Challenges. Int Clinc Med Case Rep Jour. 2024;3(7):1-7.*

Received Date: 12 July, 2024**; Accepted Date:** 15 July, 2024**; Published Date:** 17 July, 2024

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ABSTRACT

This paper presents a rare case of cribriform adenocarcinoma of minor salivary glands (CAMSG), which is a variant of polymorphous adenocarcinoma. A 79-year-old woman with a soft palate mass underwent biopsy and excision, which confirmed CAMSG through histopathological and immunohistochemical analyses. The identification of vascular invasion prompted adjuvant radiotherapy. The discussion highlights the distinct features of CAMSG, supporting its classification as a separate entity from PAC, and addresses diagnostic controversies. The paper emphasizes the importance of individual case reports for effective management and advocates ongoing research to enhance understanding of CAMSG's behavior and treatment options.

Keywords: Salivary Glands; Cribriform adenocarcinoma

INTRODUCTION

Cribriform adenocarcinoma of minor salivary glands (CAMSG) is an exceptionally rare variant of polymorphous adenocarcinoma (PAC) that was initially described in 1999. PAC, formerly known as low-grade polymorphous adenocarcinoma, is a rare type of cancer that mostly originates in the minor salivary glands.[1] CAMSG is a distinct tumor type characterized by optically clear nuclei, lobulated growth, and a cribriform-solid architecture, showcasing a high risk (>70%) of lymph node metastasis and a predilection for the base of the tongue.[2] In this paper, we report a case of a 79-year-old woman with a palate mass that was biopsied. Histopathological and immunohistochemistry suggested the diagnosis of cribriform adenocarcinoma tumor. We highlight the uniqueness and scarcity of cribriform adenocarcinoma and its histopathological, immunohistochemical, and molecular aspects.

CASE PRESENTATION

A 79-year-old woman received an otorhinolaryngological consultation regarding a lump on the right side of her soft palate that had persisted for one year. Her medical history included well-controlled high blood pressure with medication and the removal of a benign thyroid nodule. Upon examination, a 10 mm ulcerative lesion was identified on the right side of her soft palate. Flexible nasoendoscopy revealed no abnormalities, and there was no apparent cervical lymphadenopathy. Both Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) displayed a soft tissue lesion measuring 28×18 mm on the right side of the soft palate, with no definite evidence of bone involvement or cervical lymphadenopathy (Figure 1). A biopsy was performed, initially diagnosing the lesion as a Cylindroma of the soft palate. Subsequently, the patient underwent local excision.

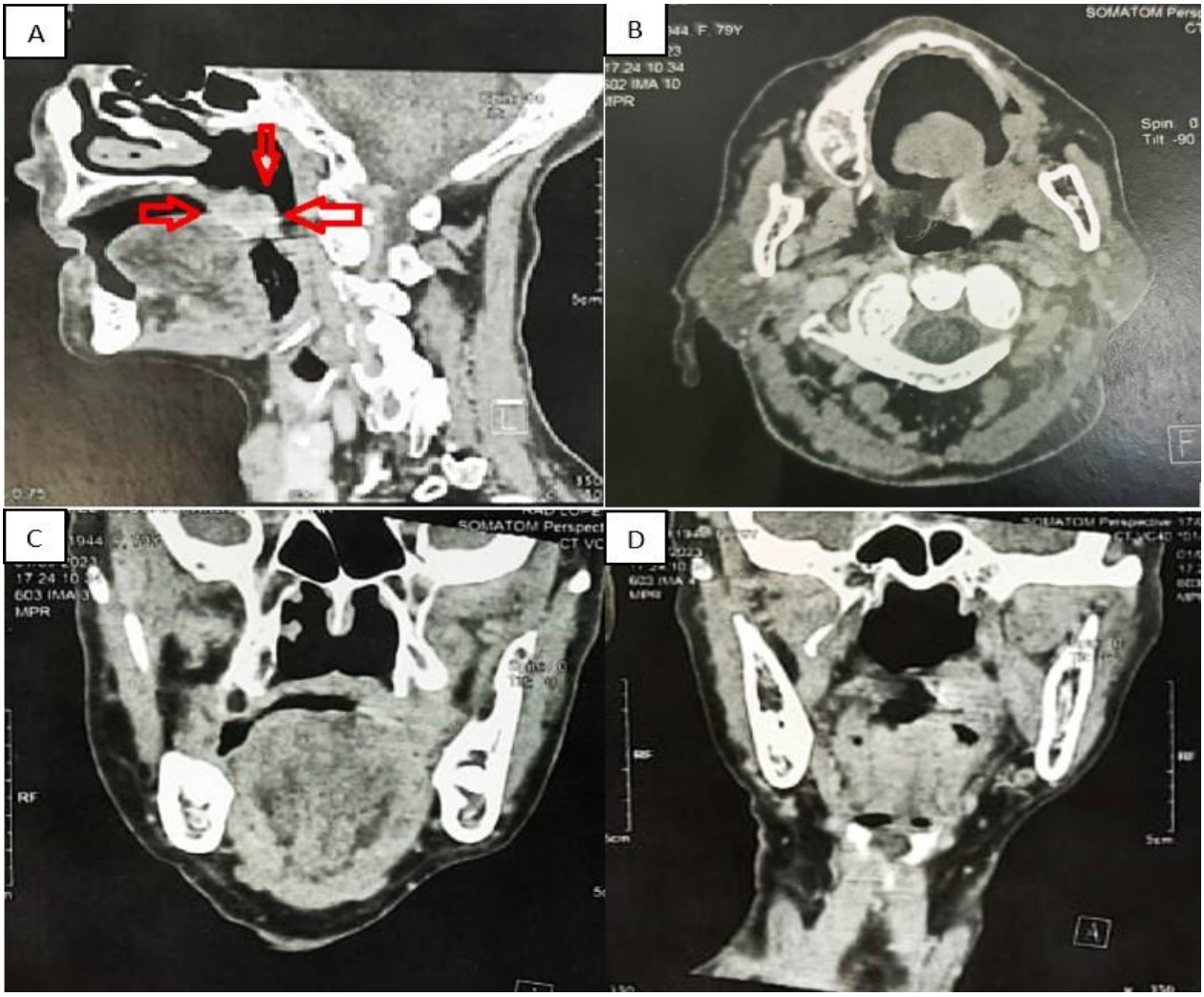

Figure 1: CT scan examination reveals a tumor occupying the soft palate. (A) The sagittal view indicates the location of the tumor with red arrows. (B) The axial view displays the localization of the tumor. (C, D) The coronal view showcases the tumor on the right side of the palate.

Histopathological examination revealed an encapsulated tumor with a multinodular pattern separated by fibrous septa. The tumor had a relatively uniform solid, cribriform, and papillary architecture. It originated from a minor salivary gland and infiltrated the respiratory mucosa of the palate. The tumor cells exhibited cubo-cylindrical characteristics with rounded to oval and optically clear nuclei, similar to those found in papillary thyroid carcinoma. The tumor invaded the surrounding capsule, contacting salivary glandular structures, and showed vessel emboli at the periphery. There was no evidence of perineural invasion, and the mitotic activity was low. No necrosis was identified (Figure 2). Based on the histological features, the diagnosis was revised to cribriform adenocarcinoma of minor salivary glands (CAMSG).

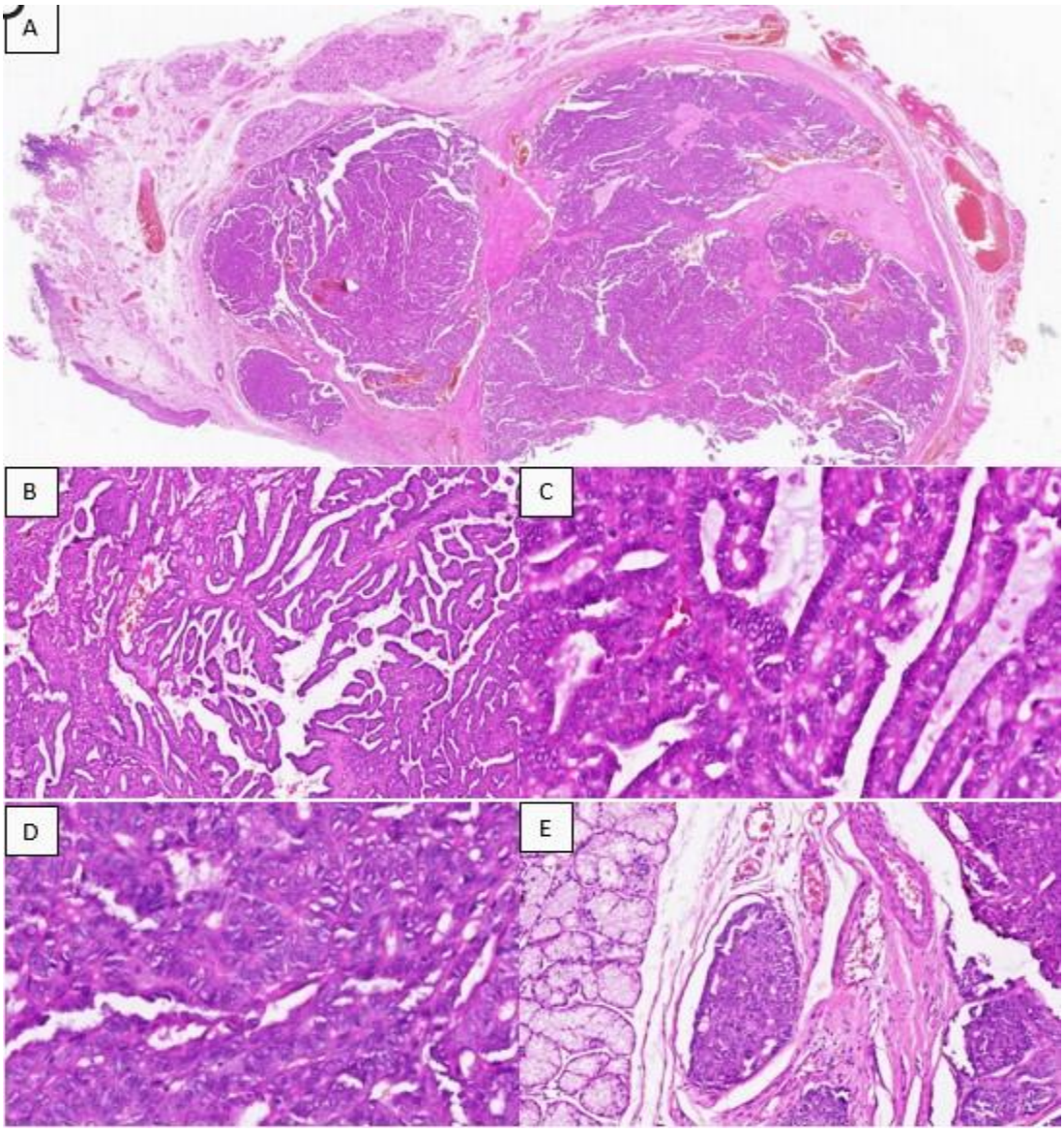

Figure 2: Histological aspects in H&E staining. (A) Low-power view of the tumor sections shows a multinodular aspect separated by fibrous septa, with tumor cells arranged in various patterns including papillary,

solid, and cribriform. The surface epithelium is noted in the lower left corner of the image. (B) H&E x 10; Tumor showing evident papillary growth. (C,D) H&E x 40; Focal papillary and pseudopapillary projections with back-to-back fusion of the glandular components there is overlap of nuclei and the nuclei are showing a clear ground-glass appearance;. (E) H&E x 40; Vascular emboli on the periphery of the tumor.

Immunoreactivity was observed with cytokeratin AE1/AE3, CK7, S100, and p63 (patchy), while it was negative for p40, thyroglobulin, and TTF1. The Ki67 index was estimated to be 20% (Figure 3). These findings, particularly the characteristic p63 positivity with concurrent p40 negativity and the absence of thyroid metastasis, supported a modified diagnosis of CAMSG.

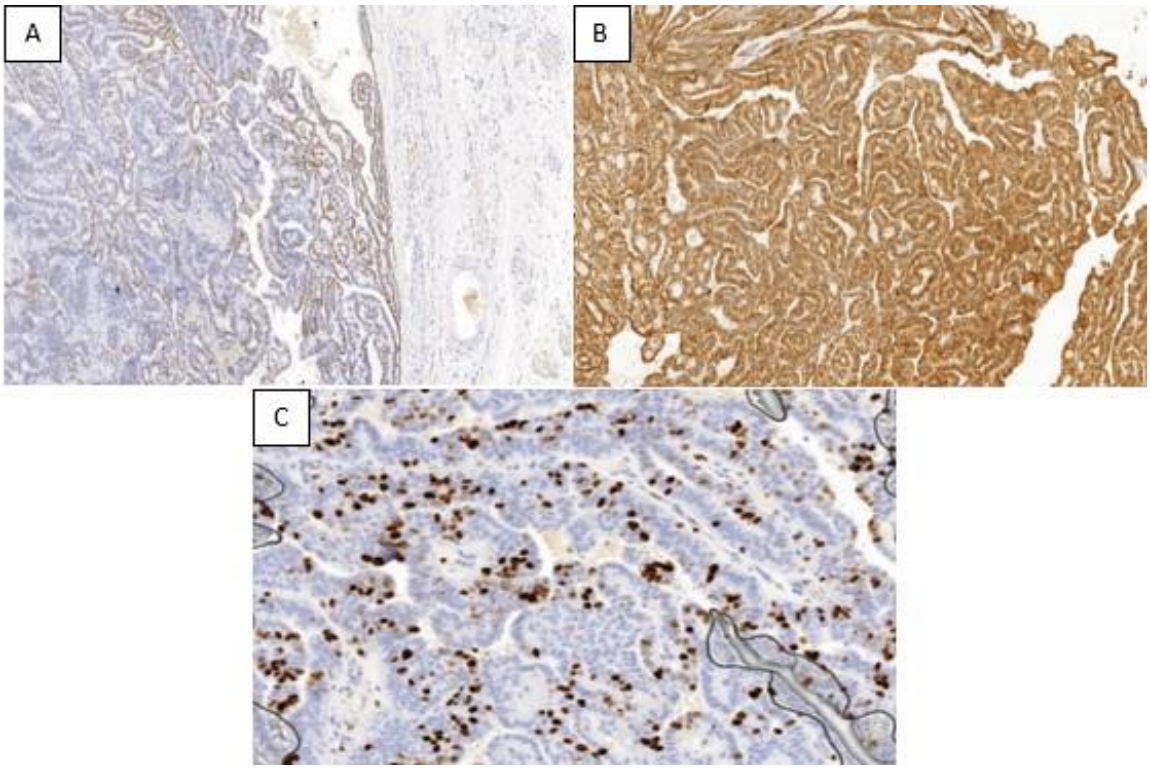

Figure 3: Immunochemistry showing (A) positive patchy expression of P63, (B) positive diffuse expression of S100, and (C) a low Ki-67 proliferation index, estimated at 20%.

The tumor extended into palatal soft tissue but did not infiltrate bone, and it appeared completely resected with untouched margins. As this low-grade salivary carcinoma showed vascular invasion without radiological evidence of metastatic disease, postoperative radiotherapy was deemed necessary. The treatment was administered using advanced conformal radiotherapy techniques, including intensity modulation such as arc therapy. Radiotherapy started five weeks after the initial treatment, with a total dose ranging between 60 and 66 Gy (2.0 Gy/fraction), administered every day from Monday to Friday over a period of 6 to 7 weeks.

DISCUSSION

Cribriform adenocarcinoma of minor salivary glands is a rare tumor that has unique characteristics. Only 58 cases of this tumor have been reported to date.[1,3,4,5,6] Initially, Michal et al. referred to it as Cribriform Adenocarcinoma of the Tongue (CAT). However, it was later discovered that the tumor originates from various minor salivary gland locations, including the soft palate, buccal mucosa, palatine tonsil area, upper lip, and even the epiglottis. The most common site of occurrence is the tongue, accounting for 60% of cases. Therefore, the tumor was reclassified as Cribriform adenocarcinoma of the tongue and minor salivary glands (CATMSG).[6]

The latest edition of the World Health Organization (WHO) 2022 Classification of Head and Neck Tumours has classified Cribriform Adenocarcinoma of Minor Salivary Glands (CAMSG) as a unique subtype within polymorphous adenocarcinoma.[7] However, some authors argue that it should be considered a separate entity.[1] This tumor is reportedly partially encapsulated with a firm consistency. CAMSG shares a histological resemblance with the conventional subtype of polymorphous adenocarcinoma (PAC), but it typically exhibits a higher prevalence of cribriform, solid, and microcystic architectural patterns. Additionally, it is characterized by glomeruloid or papillary-like structures and optically clear nuclei, reminiscent of those observed in papillary thyroid carcinoma. This feature is not observed in a classic PAC.[1,7] In contrast to the conventional subtype of PAC, CAMSG follows a more aggressive clinical course, with 7 in 10 patients presenting with nodal metastases.[1] It has been suggested that many cases of metastasizing PAC could, in fact, represent CAMSG, and that the true metastatic rate of conventional PAC could actually be much lower than reported in the literature.[1] Unlike PAC, high-grade transformation in CAMSG has not been reported to date. Despite the frequent presence of lymph node involvement at presentation, the incidence of distant metastases is exceedingly rare in CAMSG.[1]

According to the study by Skalova et al.,[4] the salient microscopic features of CAMSG were:

- The tumors were covered by intact squamous epithelium devoid of ulceration, but with varying degree of pseudoepitheliomatous hyperplasia,
- Invasive margins of the tumor with infiltration of the muscle and/or adjacent tissues.
- Presence of lymphovascular invasion,
- Predominance of cribriform and solid structures with intermingled tubular pattern,
- In solid areas, glomeruloid appearance due to detached tumor nests from the surrounding fibrous stroma by artifactual clefts,
- Overlapped nuclei, which appeared pale, optically clear and vesicular with a ground-glass appearance (cytologically resemble papillary carcinoma of the thyroid),
- Mild cellular atypia and minimal mitoses,
- 1–3 small inconspicuous nucleoli,
- Cytoplasm - clear to eosinophilic,
- Cervical lymph node metastatic deposit resembling the primary tumor.

Immunohistochemically, previous studies have reported that cytokeratin markers (AE1-3, CK7, CK8, CK18) as well as Vimentin and S-100 protein are positive. CK5/6, p53 and p63 demonstrate variable percentages of

positivity (patchy), but they were negative for p40. The Ki-67 proliferation index is low. More importantly, TTF- 1 and thyroglobulin are negative in all the tumors.[1,8]

In terms of molecular biology, the majority of PACs commonly exhibit recurring PRKD1 E710D hotspot mutations. In contrast, CAMSGs showcase rearrangements in PRKD1/2/3 genes 12. This raises the question of whether PAC and CAMSG are two tumors from the same spectrum or whether CAMSG should be regarded as a distinct entity from Polymorphous low-grade adenocarcinoma (PLGA). The distinction between PAC and CAMSG is still controversial, but rearrangements in PRKD1/2/3 genes are useful as ancillary diagnostic markers to differentiate PACs from other salivary gland tumors, such as adenoid cystic carcinoma.[1,8,11]

The differential diagnosis for cribriform adenocarcinoma of minor salivary gland involves distinguishing it from other tumors, particularly the conventional subtype of polymorphous adenocarcinoma, metastatic papillary carcinoma of the thyroid, adenoid cystic carcinoma and pleomorphic adenoma. While CAMSG is characterized by cytological monomorphism and a restricted range of growth patterns, polymorphous adenocarcinoma, conventional subtype displays various architectural appearances, including tubule, solid, cribriform, and fascicle formations. CAMSG is further identified by streaming columns of cells forming concentric whorls, resembling a target-like appearance, with occasional clear cells and mucous cells.[4,9] The nuclear similarity to papillary carcinoma of the thyroid is a unique feature of CAMSG. The absence of colloid, negative expression of thyroglobulin and thyroid transcription factor 1 and the presence of cribriform, tubular and solid growth patterns help differentiate CAMSG from metastatic papillary carcinoma of the thyroid.[4] Adenoid cystic carcinoma is distinguished from CAMSG by the presence of isomorphic basaloid tumor cells, cellular pleomorphism and higher mitotic activity. In contrast, pleomorphic adenoma, known for its morphologic diversity, exhibits combinations of gland-like epithelium and mesenchyma-like tissue, including chondromyxoid areas, squamous and osseous metaplasia, and areas of hyalinization. Ultimately, CAMSG is primarily found in the tongue, with other reported sites including the tonsil, palate, retromolar area, and upper lip, excluding the possibility of origin from thyroglossal duct remnants and pointing toward minor salivary glands.[8,10,12]

Emerging from various locations, CAMSG has the potential to form metastases, typically favoring the regional lymph nodes, although not all documented cases exhibit lymph node involvement. Conversely, nodal disease might manifest as the initial presentation. Despite the occurrence of metastatic spread, the overall prognosis remains highly favorable.[1,8]

The suggested treatment for CAMSG involves extensive surgical removal, along with elective neck dissection and additional radiotherapy as deemed necessary based on factors such as nodal involvement, margin status, perineural spread, and lymphovascular invasion.[2] There is documented evidence indicating a positive tumor response to adjuvant radiotherapy. Despite the frequent occurrence of lymph node involvement during the initial presentation, the incidence of recurrence and distant metastases is relatively low.[2] However, it is advisable to conduct long-term follow-up for CAMSG patients, as instances of recurrences and nodal metastases have been reported years after the primary tumor excision, as observed in our case.[2]

CONCLUSION

Here we present a rare case of cribriform adenocarcinoma of the minor salivary glands found in the soft palate. This tumor is classified as a relatively recent entity among salivary gland tumors, characterized by its unique

biological, histological, and immunohistochemical features. It should be recognized as a distinct tumor entity separate from PAC.

The description of individual cases of this tumor should be encouraged, helping the scientific community to better understand the behavior and therapeutic options in the management of this rare tumor.

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