CASE REPORT

Carcinoma Ex Pleomorphic Adenoma of the Palate - A Rare Encounter

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Abstract

Background: Carcinoma ex pleomorphic adenoma (Ca ex PA) is a rare malignant transformation of a benign pleomorphic adenoma, constituting about 6.2% of mixed tumors.The malignant component of Ca ex PA is most often adenocarcinoma not otherwise specified.

Case Presentation: This case report presents a 45-year-old male with an ulcerative lesion on the hard palate, initially suspected to be a minor salivary gland tumor or squamous cell carcinoma. Clinical examination revealed a non-healing ulcer and a palpable submandibular lymph node. Histopathological analysis of the biopsy showed features consistent with high-grade malignant minor salivary gland tumor, with immunohistochemical staining confirming Ca ex PA.

Management and Prognosis: The surgical resection was done with regular follow-up.

Conclusion: This tumor type, often found in the parotid glands, occasionally arises in minor salivary glands such as the hard palate. The patient's history lacked contributory factors, and the tumor presented insidiously. The case underscores the diagnostic complexity of Ca ex PA due to its varied presentation and histological features, emphasizing the importance of comprehensive diagnostic evaluation.The primary treatment involved surgical excision, with the necessity of regular follow-up to monitor for recurrence. Early diagnosis and intervention are crucial for improving prognosis and survival in patients with this aggressive malignancy.

Keywords: Carcinoma ex pleomorphic adenoma, salivary gland tumors, histopathological analysis, immunohistochemistry, surgical excision, diagnostic complexity.

Introduction

Malignant salivary gland tumors account for about 0.5 to 1.2% of all cancers and 3 to 5% of head and neck cancers. These tumors are more prevalent in women, with a male-to-female ratio of approximately 1:1.5. Malignant tumors comprise around 21.7% of all salivary gland tumors. Carcinoma ex pleomorphic adenoma (Ca ex PA) is a rare type of malignant tumor that can develop as a primary tumor or from a recurrent pleomorphic adenoma (PA). The parotid gland is the most common site for these tumors, followed by the submandibular, sublingual, and minor salivary glands.[1] Ca ex PA have also been located ectopically as well as in lung, nasal tissue and breasts. It has been referred to by various names such as carcinoma ex mixed tumor, carcinoma ex adenoma, and carcinoma ex benign pleomorphic adenoma. The definition of CA ex PA stating "carcinoma arising from a primary (de novo) or recurrent benign pleomorphic adenoma (PA)" gained widespread acceptance during the later half of the twentieth century. Notably, Gnepp compiled studies from 1953 to 1991 and presented a comprehensive review on Ca ex PA in 1993.[2,3,4] Its prevalence is reported to be 5.6 cases per 100,000 malignant neoplasms, with an annual incidence rate of 0.17 tumors per million individuals. Notably, the incidence of this tumor has shown an increasing trend over the past decade, with rates rising from 0.24 to 0.63 per 1,000,000 from 2005 to 2015. Ca ex PA is most commonly diagnosed in individuals between the ages of 60 to 80 years and is slightly

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more prevalent in women. The parotid glands are known to be the most frequent site of occurrence for this tumor, followed by the submandibular glands. Present case originates from the rare site i.e., minor mucous glands located in the hard palate. Clinically deceptive lesion witnessed by slow growth and comparatively smaller in size.[5]

Case Description

A 45-year-old male presented to our department with chief complain of ulcer on the palate present since an year. His dental, medical, personal and family history were non-contributory. The ulcer was insidious in onset with peanut size and gradually progressing to the present size, associated with pain and discomfort on taking food.

On intraoral examination a non healing ulcer was seen on the left side of the hard palate measuring approximately 3 x 2 cm, oval in shape,slightly elevated with ill defined borders.

On extraoral examination left submandibular lymph node was palpable, nontender, and firm in consistency.

The orthopantamogram showed no significant changes. Lab serum investigations were normal. Based on clinical examination Differential diagnosis of Minor Salivary Gland Tumor, Squamous Cell Carcinoma, Necrotising Sialometaplasia, Granulomatous Ulcer were considered.

Incisional biopsy was carried out and tissue biopsy was sent for histopathological examination in 10% formalin.

Gross findings

The gross specimen of 2 soft tissue bits were received, measuring approximately 1.0 x 1.0 and 0.5 x 0.5 cms, creamish white in color, irregular in shape with a rough surface and were firm in consistency, The whole of tissue bits were taken for processing.

Histopathological Findings

The microscopic examination of H &E stained sections revealed unencapsulated lesion consisting of overlying ulcerated epithelium and underlying connective tissue.The connective tissue consisted of sheets of normal mucus acini with few duct-like spaces leading to an area of atypical hyperchromatic lesional cells adjacent to the mucus acini marking the transition from normal parenchyma to malignant tumoral cells (Figure 1 A, B). The invasion of these atypical tumoral cells into the salivary gland component mimicks an invasive malignant minor salivary gland tumour.

The tumor cells were seen to be arranged in diverse patterns, including ductal patterns with eosinophilic coagulum, solid sheets, nests and papillary pattern. In higher magnification, these patterns consisted various cell types such as spindle, clear, epidermoid, mucous cells and inflammatory cells. Most of these cell populations under 40x magnification showed nuclear, cytoplasmic pleomorphism, mitotic figures, and anaplasia. Hyalinization, comedonecrosis, and perineural invasion were also evident.All of the above features were suggestive of high-grade malignant minor salivary gland tumour (figure 2 and figure 3)

Based on the presence and invasion of carcinomatous component following histopathological differential diagnosis of Poorly Differentiated Squamous Cell Carcinoma, Carcinoma Ex Pleomorphic Adenoma, High-Grade Adenoid Cystic Carcinoma, Salivary Duct Carcinoma, and High-Grade Mucoepidermoid Carcinoma, and adenocarcinoma not otherwise specified were considered.

Were used (figure 4) to confirm cell of origin that are not easily appreciated by routine H & E stain. Mucoepidermoid carcinoma and squamous cell carcinoma were excluded from the differential diagnosis viz.,

Cells	Stains	Content	DD	Result
Clear cells	-Mucicarmine -PAS	- Mucin -Glycogen	MEC	NEGATIVE
Squamous cells	-Mallory's -PAP	Keratin	SCC	NEGATIVE

Slides were subjected to immunohistochemical analysis for further investigations. With the resultant, ADCC sensitive marker i.e., c-kit was negative in the areas where cells were arranged in solid sheets. Followed by this HER2 marker was done to rule out salivary duct carcinoma, and the tumour cells in the vicinity of comedo necrosis were negative to the respective marker.

Notably there was focal positivity to S-100 indicating myoepithelial origin of tumour cells and strong positivity for GFAP confirming the diagnosis of carcinoma ex pleomorphic adenoma. Viz,

Cells	IHC marker	DD	Result
Solid sheets	C-kit	ADCC	NEGATIVE
Cells in and around comedo-necrosis	Her-2	Salivary duct carcinoma	NEGATIVE
Hyperchromatic tumoural cells	-S100 -GFAP	CA-Ex PA	- Focally positive -Strongly positive

Considering histopathological examination,special stains, and immunohistochemical parameters final diagnosis of Carcinoma Ex Pleomorphic Adenoma was made. Patient was referred to Kidwai memorial institute of oncology for further surgical procedures and advised regular follow up.

Discussion

Carcinoma ex pleomorphic adenoma (CA-ex-PA) accounts for approximately 6.2% of all mixed tumors and 3.6% of all salivary gland tumors.(4) It also constitutes 12% of all salivary malignancies. The prevalence rate of CA-ex-PA is reported to be 5.6 cases per 100,000 malignant tumors, with an incidence rate of 0.17% tumors per 1 million persons. The term 'non-invasive carcinoma ex pleomorphic adenoma' was coined by Livolsi.V and Perzin.K in 1977 to describe this malignant transformation arising from a pleomorphic adenoma. This concept was further supported by Spiro et al., who observed histological evidence of pre-existing salivary gland tumors leading to CA-ex-PA.[6]

The typical clinical presentation of CXPA is a longstanding history of PA and a sudden period of rapid growth[4].

The typical clinical presentation of Carcinoma ex Pleomorphic Adenoma (Ca ex PA) often includes a long standing history of PA with palpable firm mass in the parotid gland and sudden growth of the tumour rapidly. This type of cancer primarily affects the major salivary glands, especially the parotid and submandibular glands. However, it can also manifest in the minor salivary glands of the oral cavity, notably in the hard and soft palate, with tumors at these sites usually being smaller than those from major salivary glands.[7,8] In the present case, Ca-ex-PA manifestedon the hard palate as an ulcer ofconsiderable size. Additionally, Ca ex PA cases have been documented in other locations such as the breast, lacrimal gland, trachea, and nasal cavity. [6]

Many cases of Ca ex PA may not exhibit symptoms due to their limited invasiveness, often presenting like benign pleomorphic adenomas (PA).Similarly our case did not show any obvious hard tissue involvement/destruction in OPG. Pain can occur when the tumor invades adjacent soft and hard tissues. Facial nerve involvement can lead to facial nerve paresis or palsy. Some patients with Ca ex PA may experience skin ulceration, tumor protrusion (fungation), skin adherence, palpable lymph nodes, and difficulty swallowing (dysphagia). Other symptoms can include a swollen jaw due to bone invasion, dental pain, sudden vitality loss, and in some instances, manifestations in the lacrimal sac extending to the canaliculi and nasolacrimal duct.[9]

The macroscopic appearance of this neoplasm is determined by the proportions of its adenoma and carcinoma components. When the pleomorphic adenoma (PA) component predominates, the tumor exhibits a greyish-blue hue and may appear transparent to yellowish-white. This coloration is often associated with hyalinization and calcification within the stromal tissue. Likewise the creamish-white color of the tissue bit in present case can be attributed to hyalinisation. Conversely, when the malignant components are more prevalent, the tumor becomes extensively invasive. This leads to features like necrosis and hemorrhage, making it easily identifiable as a malignant tumor. The size of these tumors can range widely, varying from as small as one cm to as large as twentyfive cms.[1]

Carcinoma ex pleomorphic adenoma (Ca ex PA) is typically characterized by a combination of pleomorphic adenoma (PA) and carcinoma when examined microscopically. In some instances, the carcinoma component can become predominant, overtaking the entire neoplasm, making it challenging to identify the PA component solely by microscopic examination. The present case consisted 5-10% of PA like area figure 2A and maximum portion of the carcinoma component and the patient did not give any previous history of similar swelling though the lesion was chronic.Most of the times in such cases, the presence of PA may only be detected through previous biopsy records, clinicopathologic correlation, or by further sectioning of the tissue specimen. In this case a longstanding PA may have been triggered by an unknown stimulus, might have led to carcinoma. Conversely, there are cases where the tumor is mostly composed of the PA component, but with occasional scattered areas showing signs of malignant transformation. These areas exhibit features like nuclear pleomorphism, frequent or atypical mitotic figures, hemorrhage, and necrosis.[1]

The malignant component of Ca ex PA is most often adenocarcinoma not otherwise specified. Sometimes, the component may be adenoid cystic carcinoma, mucoepidermoid carcinoma, or salivary duct carcinoma as seen in our case. The other less common histological subtypes include squamous cell carcinoma, clear cell carcinoma (also seen in our case) acinic cell carcinoma, epithelial-myoepithelial carcinoma, basal cell carcinoma, myoepithelial carcinoma, The malignant component may also be a mixture of their subtypes.

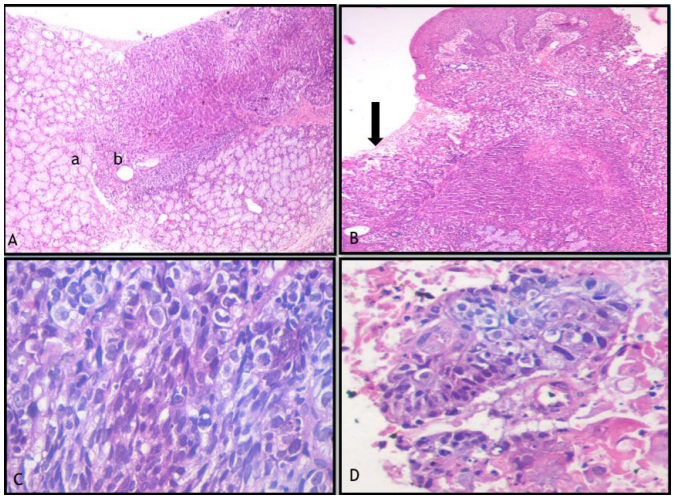

Fig. 1: H and E stained sections show **A.** normal mucus acini (a) tumor cells b (10x) , **B.** ulceration of the mucosa(black arrow) and underlyingtumour cells (10x) **C.** tumor cells in sheets and **D.**tumor cells in nests (c & d 20x)

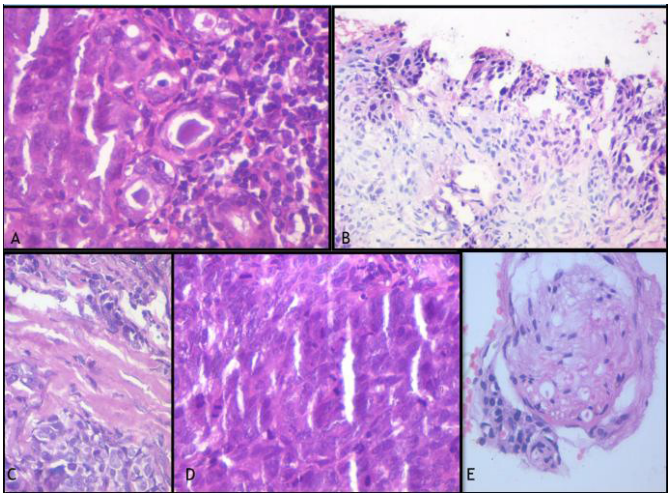

Fig. 2: H and E stained sections exhibit **A.** duct like pattern with eosinophilic coagulum(20x) **B.** papillary pattern(20x) **C.**hyalinisation (20x) **D.** mitotic figures (40x) **E.** perineural invasion (40x).

According to the World Health Organization's histologic classification from 2005, malignant derivatives of pleomorphic adenomas of salivary gland origin, termed "malignant mixed tumors," should indeed be categorized into three distinct clinical and histologic entities:

Carcinoma ex pleomorphic adenoma (carcinoma arising from pre-existing pleomorphic adenoma).

Carcinosarcoma (a true malignant mixed tumor).

Metastasizing pleomorphic adenoma.

It's noteworthy that most malignant mixed tumors fall under the category of carcinoma ex pleomorphic adenoma, while the other two types are rare occurrences.10

Carcinoma ex pleomorphic adenoma (CA-ex-PA) can be classified into three subtypes based on the extent of the carcinomatous component:

Non-invasive: The concept of non-invasive carcinoma ex pleomorphic adenoma (Ca ex PA) was initially introduced in 1977 by LiVolsi and Perzin in a study involving 47 cases of Ca ex PA[20]. This type of carcinoma is also referred to as intracapsular Ca ex PA or carcinoma in situ in the literature[21,22]. In a non-invasive Ca ex PA, the carcinoma component remains confined within the clearly defined fibrous capsule of the pleomorphic adenoma (PA). Despite marking the onset of malignant transformation, non-invasive Ca ex PA often demonstrates the benign characteristics typically seen in PA.[11] It exhibits well-defined borders with minimal nuclear pleomorphism and may exhibit a myxoid area with a mix of cellular and acellular regions. [6]

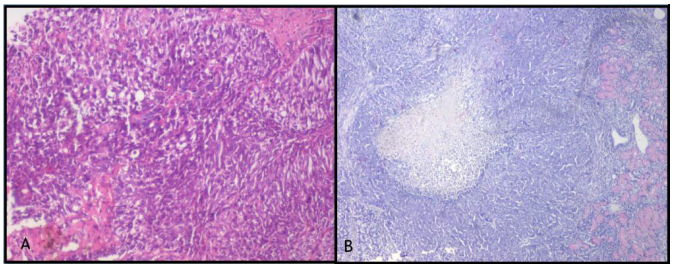

Fig 3: A. lesional spindle shaped cells (20x) **B.** comedonecrosis (10x)

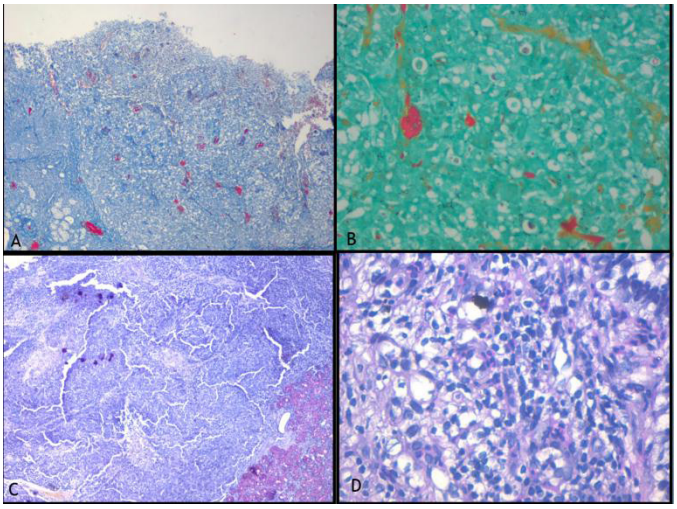

Fig. 4: A. mallory's stain (epidermoid cells) **B.** pap stain (epidermoid cells) **C.** mucicarmine stain **D.** PAS stain (clear cells) (magnification (a & c 10x) (b & d 20x 20x)

Minimally invasive:Indicates less than 1.5 mm penetration of the malignant component into the extracapsular tissue.[6] From a histological perspective, minimally invasive Ca ex PA closely resembles intra-capsular Ca ex PA, exhibiting a mix of tumour areas, intra-ductal carcinoma areas, and carcinoma areas.[1]

Invasive: Shows an invasion greater than 1.5 mm into neighboring tissues with non-defined margins, high nuclear pleomorphism, and adjacent perivascular and perineural infiltration.[6]

The immunohistochemical profile of carcinoma ex pleomorphic adenoma (Ca ex PA) reveals a strong and diffuse expression of pan-cytokeratin markers such as AE1–AE3 and CAM5.2, as well as CK7, CK8, CK18, CK19, and epithelial membrane antigen (EMA). Additionally, basal/myoepithelial cell markers like p63, smooth muscle actin, CK5/6, and CK14 may be observed focally in the basal/myoepithelial cells surrounding residual foci of non-invasive Ca ex PA .[12]

Differential diagnosis includes recurrent pleomorphic adenoma that is commonly multinodular; and may show numerous disconnected nodules with no obvious capsule, simulating invasion. A history of incompletely resected or previously recurrent pleomorphic adenoma is a clue to the diagnosis. In the case of de novo carcinoma, identification of residual pleomorphic adenoma (or a history of recurrent / incompletely excised pleomorphic adenoma) is essential for diagnosis of carcinoma ex pleomorphic adenoma. PLAG1 and HMGA2 genetic aberrations are seen in carcinoma ex pleomorphic adenoma but not its malignant de novo counterparts. Metastatic carcinoma have a history of other primary head and neck malignancy and absence of pleomorphic adenoma component.[13]

The treatment for carcinoma ex pleomorphic adenoma typically includes surgical excision, which may be ablative in nature such as lobectomy or gland extirpation. Reconstructive surgery might follow the initial excision depending on the extent of the surgery and the patient's condition. Given that the parotid gland is frequently involved, the surgical procedure often entails parotidectomy.[12]

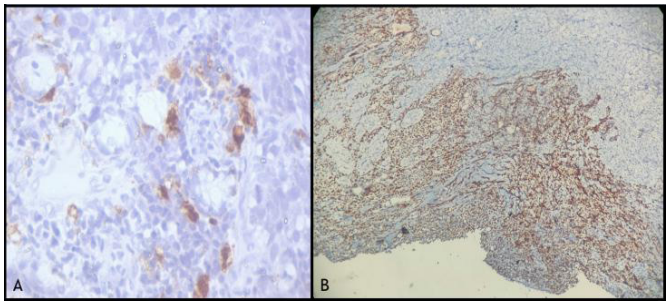

Fig. 5 A: S-100 showing focal positivity (20x) **B:** diffuse positivity seen with GFAP (10x)

Conclusion

In conclusion, the case report highlights a rare occurrence of carcinoma ex pleomorphic adenoma originating from the hard palate. This tumor presents as an innocuous ulcer and turning out to be a destructive entity whose early diagnosis and intervention is crucial for predicting the prognosis and betterment of the survival of the patient. The diagnostic challenges associated with carcinoma ex pleomorphic adenoma stems from its clinical presentation, site and varied histological findings, which can complicate its identification and management. Surgical excision remains the primary treatment modality, often followed by adjuvant therapies like radiotherapy or chemotherapy to improve survival rates. The case underscores the importance of accurate diagnosis for this aggressive form of tumor to achieve favorable patient outcomes.

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