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Case Report

A rare case report on carcinoma ex pleomorphic adenoma and mini review of histological features

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ABSTRACT

Carcinoma ex pleomorphic adenoma (Ca ex PA) is a rare malignancy that represents a transformation of a primary pleomorphic adenoma (PA), or carcinoma arising from primary (de novo) or recurrent or pre-existing pleomorphic adenoma (PA). Pleomorphic adenoma is a benign mixed common neoplasm that arises from the major salivary gland. Here we are presenting a case report of a 60-year-old female patient with a history of swelling in her right parotid region for 1 year. After a thorough clinical and histological examination it is diagnosed as carcinoma ex pleomorphic adenoma (Ca ex PA). In our case report we are more emphasizing the histological behavioral pattern of Carcinoma ex pleomorphic adenoma in preexisting pleomorphic adenoma (Ca ex PA) as distinctive histological features of this rare tumor play an essential role in the diagnosis of this tumor and thus, aid in the correct treatment plan and better prognosis.

1. Introduction

The parotid gland is the largest gland out of the 3 Major salivary (i.e., Submandibular, and sublingual Glands) along with other Minor (i.e., Labial, Lingual, Palatal, Buccal, Gloss palatine, and Retromolar Glands) salivary glands. Parotid Gland is an exocrine gland (i.e., having an extended duct known as Stenson's Duct), located superficially (known as Parotid Space) outside the oral cavity in front of the external ear.[1,2] Salivary gland diseases, and tumors constitute a diversity of lesions with great morphologic variation thus posing difficulty in diagnosis. It can arise from major as well as minor salivary glands.[3] Pleomorphic adenoma (Mixed Tumor) is also one of the most common benign mixed neoplasms which mainly arise from major salivary glands (53% to 77% occurs in the parotid gland).[4] It is entirely of epithelial origin and the term mixed tumor is used as a descriptive term indicating the histologically morphologic diversity features because of differentiation of tumor cells/Metaplasia in fibrous, Osseous, and chondroid areas.[3] It rarely undergoes a malignant transformation.But malignant changes that occur in pleomorphic adenoma will be because of long-standing adenoma, recurrence of tumor, radiation therapy, old age, and tumor size. The risk of developing malignancy in pleomorphic adenoma is about 1.5% but increases to 9.5% for a duration of 15 years.[4,5]

The Carcinoma ex pleomorphic adenoma (Ca ex PA) is defined as a carcinoma arising from a primary (de novo) or recurrent benign pleomorphic adenoma (PA),[6–8] that is, it evolves from a pre-existing benign pleomorphic adenoma. Carcinoma ex pleomorphic adenoma (Ca ex PA) is an infrequent aggressive malignancy that accounts for approx. 3.6% (range, 0.9%–14%) of all salivary neoplasms and for 11.7% (range, 2.8%–42.4%) of salivary malignancies.[9]

Here, we are presenting a rare case report of 60 years old female patient who visited our clinic with a chief complaint of painless swelling in the right parotid gland region in the past 1 year. On taking history it was revealed that swelling

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was small and inconspicuous initially and grew gradually to a current size 5.1 x 2.0 x 3.2 cm within 1 year. Initially, an incisional biopsy was performed and diagnosed as Pleomorphic adenoma (PA) consequently excisional biopsy was performed and Carcinoma ex pleomorphic adenoma (Ca ex PA) was diagnosed.

2. Case Report

A 60-year-old female patient reported to our clinic with a chief complaint of swelling in her right parotid gland region for 1 year. The swelling was initially small and gradually increased within 1 year. The growth was painless, solitary, well-delineated, intermittent, and slow in nature.

On inspection, it is found that the right parotid gland region was slightly deformed due to swelling. The patient did not show any sign of facial palsy or ear sensory disturbances. There were no signs of any elevation of the right ear lobe.

On palpating, the swelling was found to be firm in consistency and fixed to the deep planes of parotid glands. The superficial skin was smooth, lobulated with no ulceration present. The lymph nodes were non-tender.

The patient was instructed to undergo an excisional biopsy of the same region. On Gross examination, we received a single bit soft tissue specimen with rough surface texture area, grayish in color, partially encapsulated in some areas, measuring approx. 2x2x1 cm in size, firm in consistency (Figure 1). The tissue is then longitudinally cut into two sections (Figure 2) and one of the tissues was kept for routine H & E routine procedure.

The H & E stained tissue section were then examined microscopically to give a confirmed diagnosis. All the tissue sections examined are shown in this case report (Figures 3, 4, 5, 6, 7, 8, 9 and 10). Based on clinical and histopathological examination of all the sections, the lesion was diagnosed as carcinoma ex pleomorphic adenoma.

On histopathological Examination, the given H & E stained soft tissue sections reveal incompletely encapsulated lesion tissue (Figure 3) and cystic degeneration (Figure 4) indicating long-standing tumors. The given section also shows large areas of dyskeratosis with various other dysplastic features like cellular and nuclear pleomorphism, Hyperchromatism (Figures 5 and 10). It also shows diverse histologic patterns arranged in sheet, cords, Islands, trabeculae, rosette, myxoid degeneration (Figure 6), osteoid formation (Figure 7), carcinomatous changes like the formation of keratin Pearls (Figure 8), and duct-like structures (Figure 9) which is a classical feature of carcinoma ex pleomorphic adenoma.

3. Discussion

Salivary Gland diseases and tumors comprise a heterogeneous group of entities of diverse etio-pathogenic backgrounds. Most salivary gland diseases have specific and non-specific developmental, inflammatory, immunological, or metabolic origins.[10]

Pleomorphic Adenoma (PA) or Benign Mixed Tumor is the most common neoplasm of the salivary gland which is histologically characterized by the complex intermingling of epithelial components and mesenchymal areas.[10] It consists of cells exhibiting the ability to differentiate between epithelial (Ductal and Non-Ductal) cells and mesenchymal (Chondroid, Myxoid, and Osseous) cells.

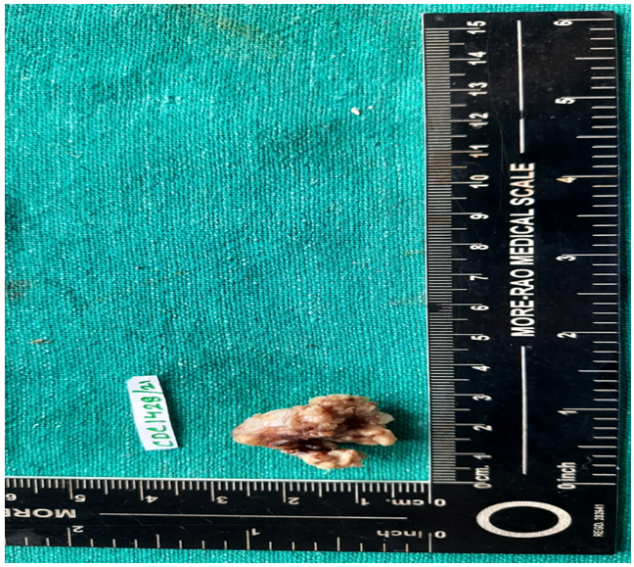

Figure 1: Under this figure single soft tissue specimen with encapsulated mass is seen measuring approx. 2x2x1 cm in size

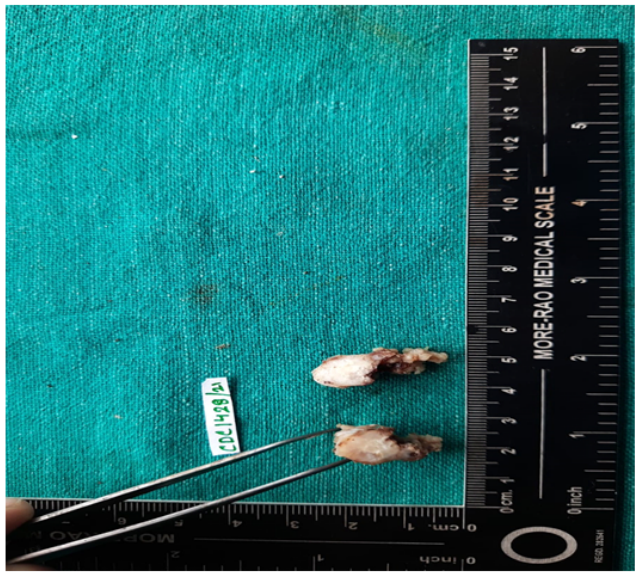

Figure 2: Same soft tissue specimen is splatted into longitudinal section and sent for routine H & E staining procedure

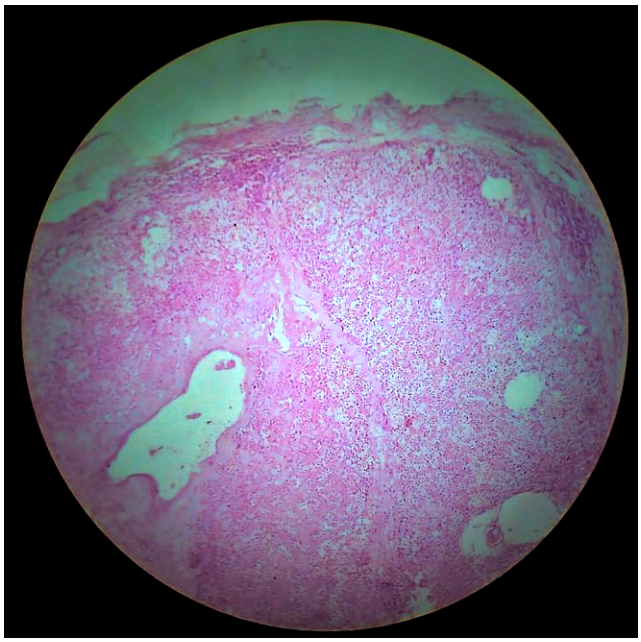

Figure 3: H&E (10x magnification) stained section reveals lesioned tissue showing capsule partially encapsulating underlying connective tissue

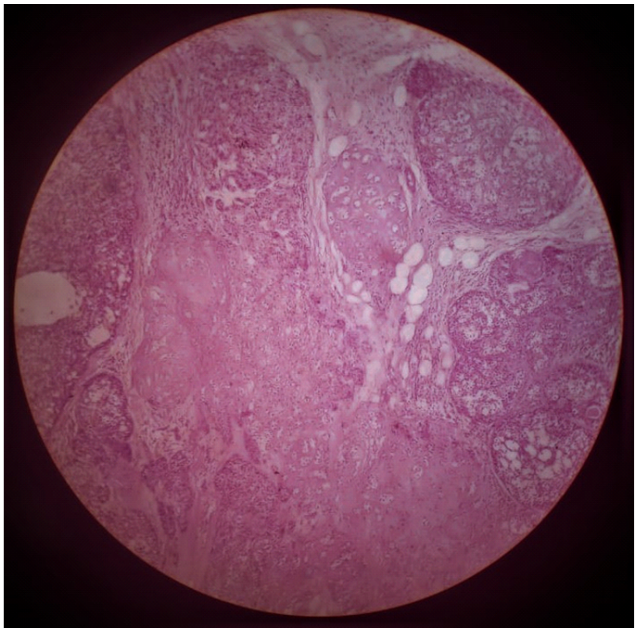

Figure 5: H&E (10x magnification) showing morphologic diversity in the form of rosette pattern, large areas of Dyskeratosis along with areas of cellular and nuclear pleomorphism

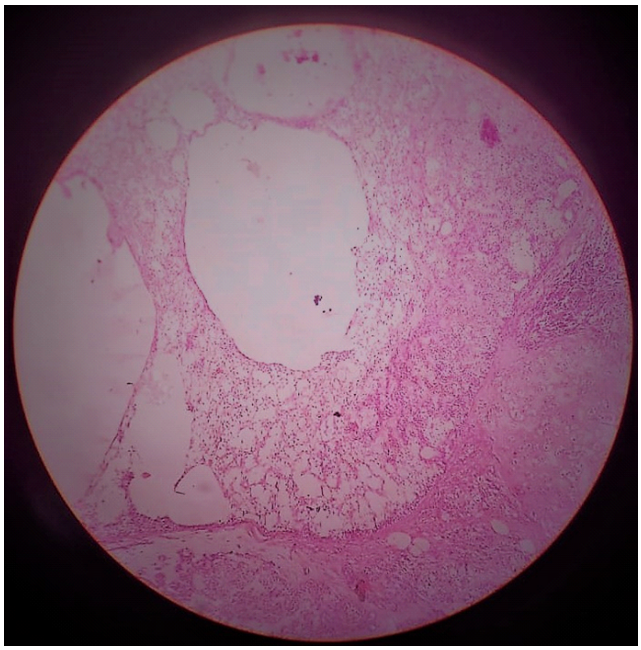

Figure 4: H&E (10x magnification) showing Cystic Degeneration thus indicating long term tumor

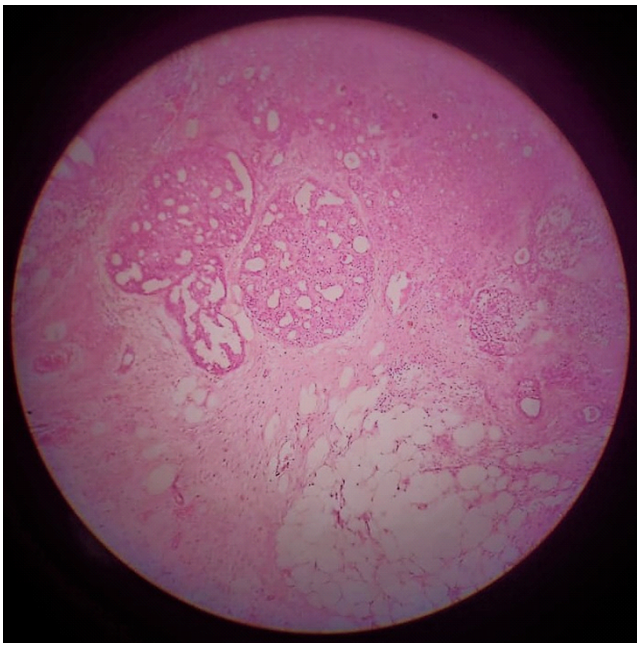

Figure 6: H&E (10x magnification) showing ductal pattern, myxoid degeneration along with adipose tissue

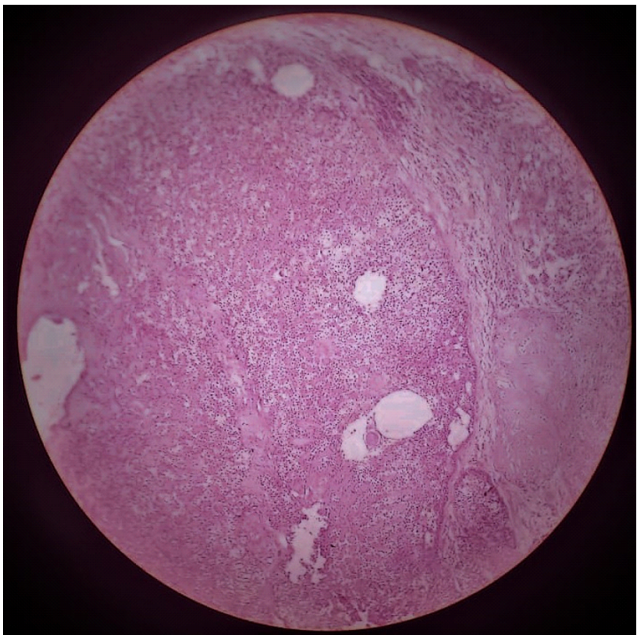

Figure 7: H&E (10x magnification) showing Osteoid formation within the given section

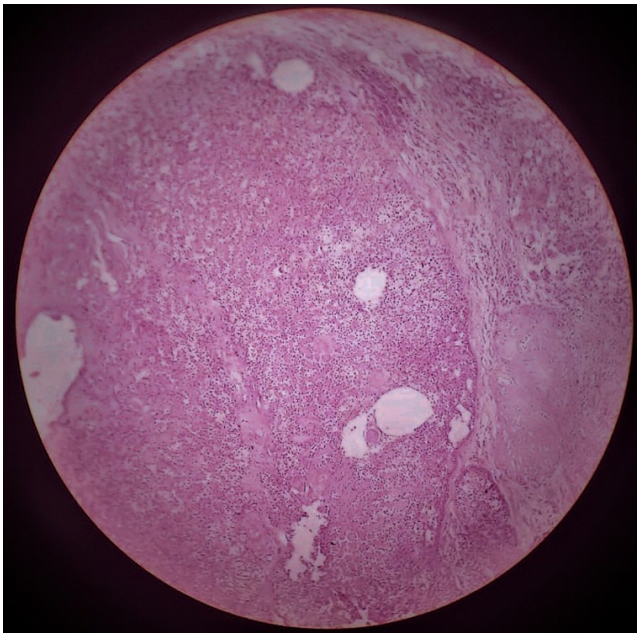

Figure 8: H&E (10x magnification) showing increased dysplastic area present in the core of regional tissue, larger area revealing well defined rosette pattern, carcinomatous changes including keratin pearls, nuclear pleomorphism within the given section

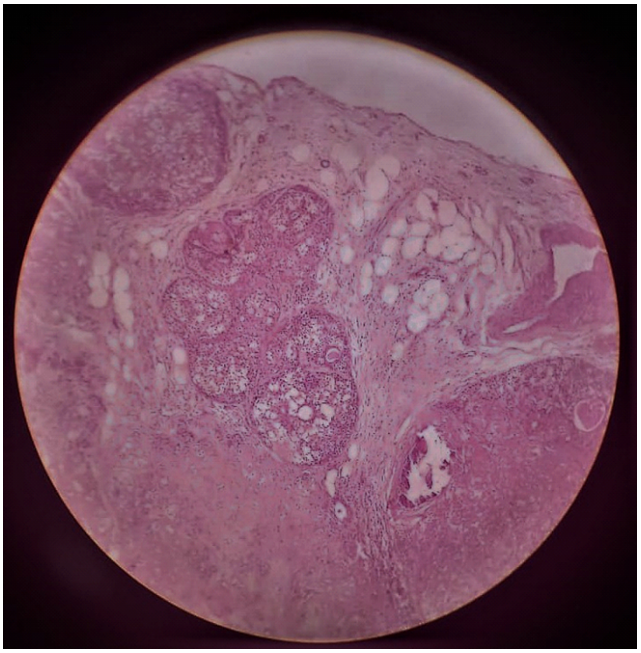

Figure 9: H&E (10x magnification) showing ductal pattern, myxoid degeneration, adipose tissue, moderate to severe inflammatory cells within connective tissue stroma.

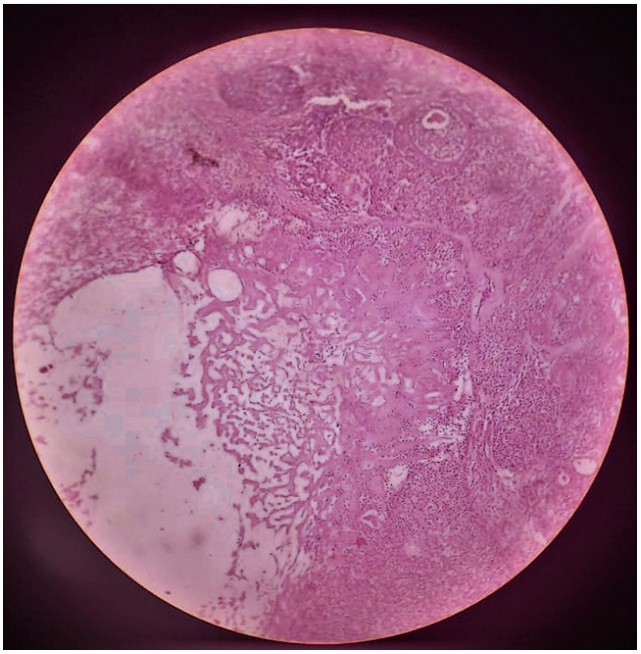

Figure 10: H&E (10x magnification) showing diversity of tumor cells in the form of dysplastic areas along with cellular and nuclear pleomorphism.

This tumor is not a 'mixed' tumor in the true sense of being teratomatous or derived from more than one primary tissue.[11] Mixed tumor is simply used as a descriptive term for a neoplasm that characteristically shows combined features of epithelium and connective tissue-like growth. Morphologic diversity is i.e., a hallmark of the tumor composing of glandular epithelium and myoepithelial cells within the mesenchyme-like background.[3]

The pathogenesis of pleomorphic adenoma reveals that these tumor cells undergo metaplasia, because of which these cells exhibit different histopathological pictures consisting of fibrous, myxoid, chondroid, osseous, and hyalinized areas. These different morpho differentiative pictures can be explained by the reserve cell theory given by Batsakis and his associates according to which the intercalated duct reserve cell is the histogenesis precursor of Pleomorphic adenoma. Recent concepts reveal that this unique tumor revolves around both myoepithelial cells and the reserve cells of intercalated ducts. Also, some studies prove that there is a chromosomal aberration in the long arm of 8 and 12 and chromosomal translocations between chromosomes 3 and 8 thereby juxtaposing the PLAG 1 gene with the ß-catenin gene. Because of this arrangement, the ß-catenin pathway gets activated resulting in an inappropriate division of cells.[12]

PLAG1 encodes a nuclear oncoprotein (PLAG1) that functions as a DNA-binding transcription factor.[13–15] Several genes upregulated by PLAG1 are growth factors, including human IGF-II. Activation of the IGF-II signaling pathway is one of the main molecular mechanisms mediating PLAG1-induced oncogenesis.[14–17]

Carcinoma ex pleomorphic adenoma (Ca ex PA) is a rare malignant transformation of a benign primary pleomorphic adenoma (PA).[18] The pathogenesis of Ca ex PA can be explained by 2 hypotheses: First, these tumors are malignant in nature since from the origin and secondly these tumors undergo the carcinomatous transformation of a primary tumor (de novo) or recurrent pleomorphic adenoma.[9,19] The incidence of Carcinoma ex pleomorphic adenoma accounts for 5 to 25% of primary pleomorphic adenoma (PA).[20,21] Misdiagnosis is common, as the residual pleomorphic adenoma component may be small, and therefore missed, on histological analysis. The most common clinical presentation of Carcinoma ex pleomorphic adenoma is of a firm mass in the parotid gland. The entity is difficult to diagnose preoperatively. Pathological assessment is the gold standard for making the diagnosis. Treatment for Carcinoma ex pleomorphic adenoma often involves an ablative surgical procedure, which may be followed by radiotherapy. Overall, patients with Carcinoma ex pleomorphic adenoma have a poor prognosis. Accurate diagnosis and aggressive surgical management of patients presenting with Carcinoma ex pleomorphic adenoma can increase their survival rates.[22]

3.1. Histo-pathological variants of carcinoma ex pleomorphic adenoma

The proportion of the adenoma and carcinoma components determines the macroscopic features of this neoplasm.[22] Based on the presence and degree of invasion of this carcinomatous component outside the fibrous capsule, WHO divided Ca ex PA into 3 groups.[19]

3.2. Non-invasive Ca ex PA (Also known as intra-capsular CA ex PA carcinoma in situ)

The non-invasive Ca ex PA concept was first introduced by LiVolsi and Perzin (1977). The carcinoma component in a non-invasive Ca ex PA is confined within the well-defined fibrous capsule of the PA.[23] (Figure 11). Clinically, it shows no local recurrence or distant metastases suggesting its non-aggressive nature.[24] Although non-invasive Ca ex PA marks the beginning of the malignant transformation, it tends to exhibit the benign behavior of PA.[8]

Minimally invasive Ca ex PA - When the malignant component of Ca ex PA undergoes <1.5 mm penetration into extracapsular tissue, it is classified as minimally invasive Ca ex PA.[19,25]

Invasive Ca ex PA is defined as the invasion of malignant components greater than 1.5 mm from the tumor capsule into adjacent tissue.[19,25,26] The PA areas are composed of nodules of hyalinized tissue with sparse, scattered ductal structures as the carcinoma areas increase in proportion. Although the invasive carcinoma areas are very similar to those described in intra-capsular Ca ex PA carcinoma areas, there is an increased tendency for malignant cells to decrease in size and migrate away from the origin.[26]

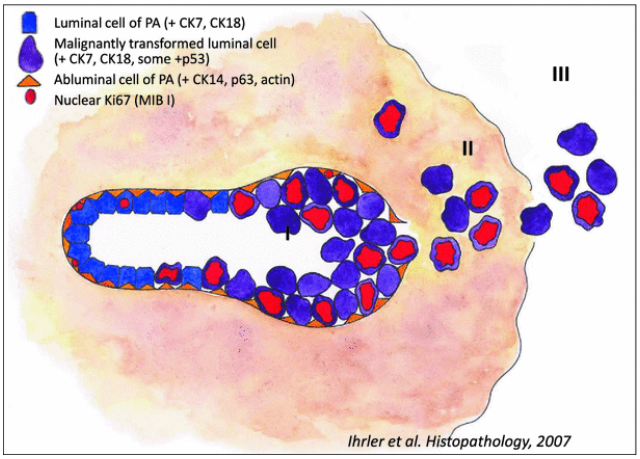

Figure 11: Diagram showing progression of carcinoma ex pleomorphic adenoma. I Preexist tubules of Pleomorphic Adenoma partly replaced by malignant epithelial cells. II Rupture of basal membrane with extra tubular extension but still confined within the capsule of PA. III Extracapsular spread with infiltration of surrounding tissues. Courtesy by Dr. S.Ihrler.[27]

Table 1: A case study on carcinoma ex pleomorphic adenoma (Ca ex PA) by different authors in the last 20 years

Authors	Year	No. of Cases
Livosi and Perzin[23]	1977	47
Brandwein et al.[29]	1997	12
Olsen et al.[9]	2001	73
Felix et al.[30]	2002	1
Altemani et al.[26]	2005	10
Ihrler et al.[25]	2007	19
Katabi et al.[31]	2010	13
Weiler et al.[32]	2011	19
Di Palma et al.[24]	2012	11
Hashimoto[33]	2012	31
N. Chooback[34]	2017	1
Deepak Khanna et al[35]	2019	1
Ji-Kwan Kim[36]	2020	1
Can Wang et al[37]	2021	212
Zhang P[38]	2019	64

Ca ex PA can also be divided into 2 subtypes based on morphological and immunohistological features- First those with only epithelial (luminal) malignancy and those with myoepithelial (non-luminal) malignancy. Demasi et al. found that 75% of the cases of Ca ex PA, are found to be a luminal malignancy.[28]

Altemani et al. observed that the malignant transformation of myoepithelial cells results in the absence of ductal structures. Ca ex PAs with myoepithelial differentiation were usually frankly invasive and were found in both the major and minor salivary glands.[26]

It occurs more frequently in the 5^{th} and 6^{th} Decade of life (Mean Age 40 Years), more common in females with 60-65% in the parotid gland, 50% in the submandibular gland, 25% in the sublingual gland. In Minor salivary gland neoplasm, 25% occurs in the upper lip and 10% in the cheek.[10]

Investigation of Carcinoma ex pleomorphic adenoma includes FNAC, MRI, special stain to differentiate myxoid, osseous, or chondroid tissues of neoplasm and Immunohistochemistry (IHC).[24]

The immunohistochemical profile of Ca ex PA shows diffuse and strong expression of pan-cytokeratin (AE1–AE3 and CAM5.2), CK7, CK8, CK18, CK19, and epithelial membrane antigen (EMA). Staining for basal/myoepithelial cell markers like p63, smooth muscle actin, CK5/6, and CK14 may be focally present in the basal/myoepithelial cells surrounding residual foci of non-invasive CXPA.[24]

Treatment for carcinoma Ex Pleomorphic Adenoma involves an ablative surgical excision (Lobectomy or Gland Extirpation) which may or may not be followed by reconstructive surgery. Since the parotid gland is predominantly affected, ablative surgery often involves parotidectomy.[24]

Table 1 mention the number of cases of occurrence of carcinoma Ex Pleomorphic Adenoma in the last 20 years. This indicates that carcinoma Ex Pleomorphic Adenoma is a rare tumor but more aggressive than PA.

4. Conclusion

Carcinoma ex Pleomorphic adenoma is one of the common and aggressive neoplasms which arises from a preexisting pleomorphic adenoma. Because of its aggressive and unpredictable nature, it constitutes a great diagnostic dilemma for clinicians as well as pathologists and consequently, leads to a poor prognosis. So, it is important to assess the growth of tumor pathologically and histologically for making correct clinical and histopathologic diagnoses along with an early diagnosis with a high index of suspicion. Treatment involves surgical procedures, followed by radiotherapy. Till now, there are no guidelines available for the management of this tumor. Metanalysis can be employed for the best outcomes of this aggressive tumor.

5. Source of Funding

None.

6. Conflict of Interest

None.

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