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AMELOBLASTIC CARCINOMA: A HIDDEN MALIGNANCY UNVEILED

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ABSTRACT:

Ameloblastic carcinoma refers to tumors exhibiting ameloblastomatous differentiation and displaying cytological features of malignancy, with or without metastasis. A 52 years old male patient visited with a chief complaint of mobile tooth in his right back tooth region for past 3 months. On examination a grayish-white patch intermixed with erythematous areas was observed on the right buccal mucosa in relation to 47 and 48 along with Grade III mobility, and extraorally a diffuse swelling was evident at the left lower border of the mandible. OPG revealed an ill-defined radiolucency of right side of mandible from mesial root of 48 extending to involve angle of the mandible. Based on histopathological and immunohistochemical examination a final diagnosis of Ameloblastic Carcinoma was made.

Keywords: Ameloblastic Carcinoma, Ameloblastoma, IHC, Malignant ameloblastoma

1. INTRODUCTION:

Ameloblastic carcinoma (AC) is a malignant neoplasm of the jaw bones with an incidence of 1.6-2.2% among all odontogenic tumours and represents less than 1% of ameloblastoma. The term “ameloblastic carcinoma” was first coined by Elzay (1982). Slootweg and Müller (1984) recognized the AC as a separate entity with added cytologic features of malignancy in ameloblastoma. AC is a relatively rare type of tumor which, according to the World Health Organization (WHO), is a carcinoma that can be classified as either metastasizing ameloblastoma or AC. Ameloblastic carcinoma shows features of dysplasia histologically and features of malignancy clinically, hence treatment approaches differs between ameloblastic carcinoma and ameloblastoma can be challenging (1).

As per the WHO 2017 Classification, there are two types of AC, Primary and Secondary. Primary form arise de novo, whereas the secondary type arises from preexisting ameloblastoma with malignant transformation (1). The term "Ameloblastic carcinoma" refers to tumors exhibiting ameloblastomatous differentiation and displaying cytological features of malignancy, with or without metastasis. Conversely, the term "Malignant ameloblastoma" is used for ameloblastomas that metastasize without exhibiting histological signs of malignancy in either the primary or metastatic sites.

AC predominantly affects the mandible, though it can also involve the maxilla. It is more commonly seen in males. The typical age range is between the fifth and seventh decades of life, with an average age of 53.5 years. However, some cases have been reported as early as the second decade. AC diagnosis is based on the evaluation of clinical signs and symptoms, which include pain, facial swelling, ulceration, trismus, paresthesia and dysphonia, as documented in existing literature (2).

Four clinical criteria given by Hall et al., are particularly useful in diagnosing ameloblastic carcinoma (AC): rapid growth, local aggressiveness, tendency to perforate the cortex, and the presence of pain and paresthesia, which help distinguish AC from its benign counterparts. Radiographically, an ill-defined unilocular or multilocular radiolucent lesion with poorly defined borders are seen and often accompanied by local radiopacities resembling dystrophic calcifications. Root resorption and loss of lamina dura are additional radiographic features (3). The definitive diagnosis of AC relies on histopathological features along with immunohistochemical studies being essential for differentiating AC from other odontogenic tumors.

CASE REPORT

A 52 years old male patient visited with a chief complaint of mobile tooth in his right back tooth region for past 3 months. Patient gave history of pain and difficulty in mouth opening for past 3 months and the pain was dull, continuous, aggravated on chewing food and relieved on its own. Patient gave history of smoking tobacco and alcohol consumption habit for past the 25 years. During the intraoral examination, a grayish-white patch intermixed with erythematous areas was observed on the right buccal mucosa in relation to 47 and 48. Grade III mobility in 48 and generalized attrition of teeth and limited mouth opening was observed. On extraoral examination, a diffuse swelling of size 1.5cmx2cm was evident at the left lower border of the mandible, which was slightly tender on palpation. On radiographic examination, OPG revealed an ill-defined radiolucency of right side of mandible from mesial root of 48 extending to involve angle of the mandible (Fig 2). Incisional biopsy was done and multiple bits of soft tissues were submitted for histopathological examination. The bits were grayish brown in color, soft to firm in consistency, irregularly shaped and with smooth surface. All the Soft tissue specimens along with the soft

tissue scrapped off from the tooth were routinely processed, sectioned and stained for histopathological examination.

Fig 1: Intraoral clinical image

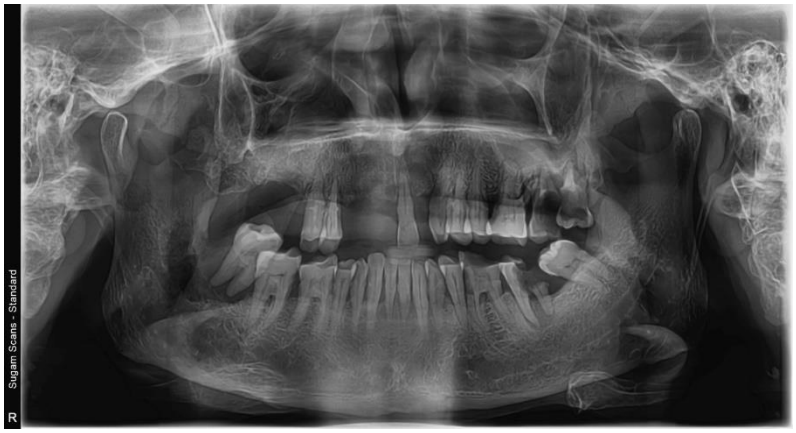

Fig 2: OPG

Microscopic examination of the H & E stained sections of the soft tissue specimen revealed bits of fibrocellular connective tissue areas with plump fibroblasts and dispersed islands of tumor resembling odontogenic epithelium. Abundant vascular slits distributed throughout the connective tissue with focal collections of inflammatory cells chiefly lymphocytes, macrophages, epitheloid cells and scattered plasma cells. The tumor islands showed peripheral columnar, cuboidal and squamous cells and the central area is composed of polyhedral and stellate reticulum like cells. Many islands showed central cell undergoing squamous metaplasia. Multinucleated giant cells were seen scattered throughout the connective tissue areas many of them seen within the lumen of blood vessels. Within the tumour islands cells were seem to undergo degeneration. Features of dysplasia like enlarged dark nuclei, reversed nuclear cytoplasmic ratio and frequent mitotic figures were seen within the tumour islands. Areas of necrosis and areas of hemorrhage were seen in focal areas (Fig 3). Based on these findings, a diagnosis of “Ameloblastic Carcinoma” was considered. Immunohistochemistry (IHC) was performed for confirmatory. IHC showed positivity for CK-14, CK-19, intense positivity for Ki-

67 (50% proliferative index) and negative for CK-7 (Fig 4). Based on these, a definitive diagnosis of "Ameloblastic carcinoma" was arrived.

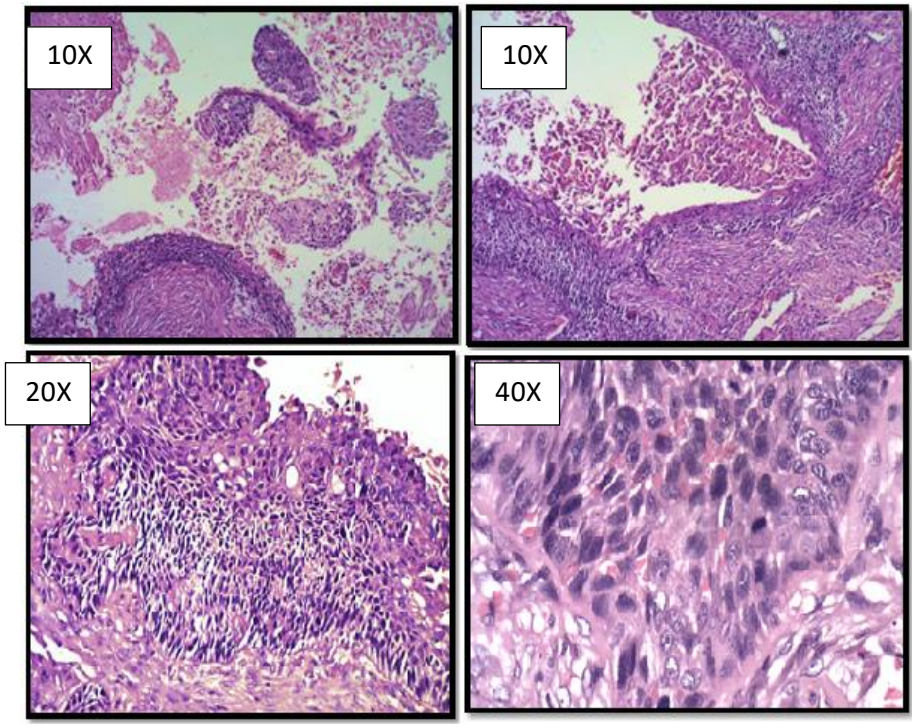

Fig 3: Microscopic features

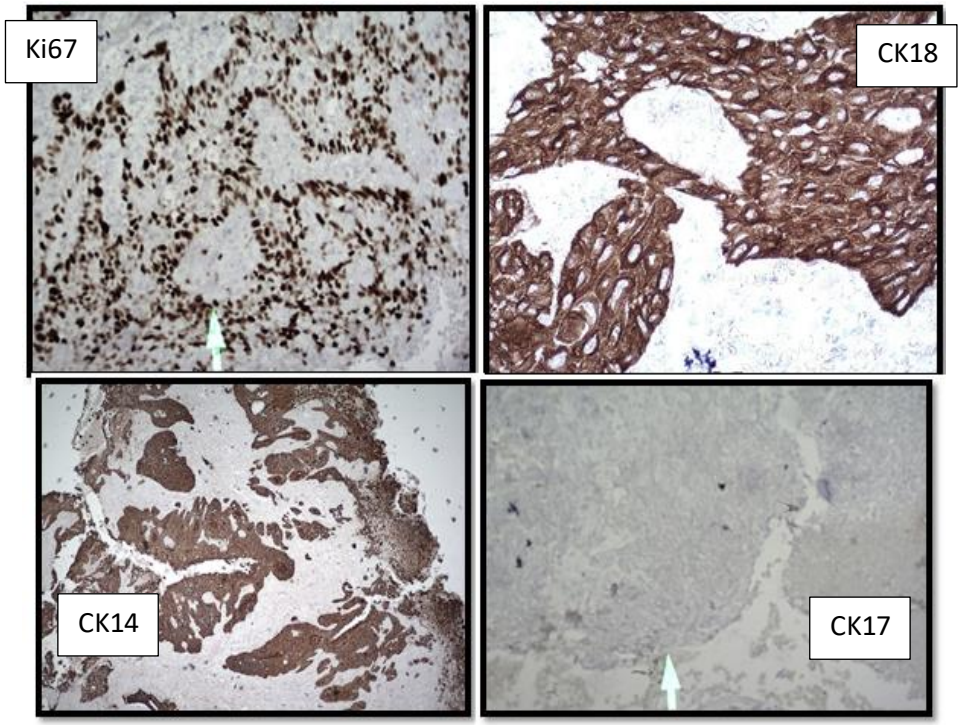

Fig 4: Immunohistochemistry

2. DISCUSSION:

Ameloblastic carcinomas (AC) are highly uncommon malignant tumors of odontogenic epithelial origin, which can develop either spontaneously or from a pre-existing odontogenic lesion. Although AC is less common than ameloblastoma, it remains the most prevalent malignant OT. The pathophysiological mechanisms underlying its development are not well understood, leading to significant controversy regarding its biological behavior. It has been proposed that the sequential carcinogenesis of ameloblastoma involves multiple genetic defects.

Principally, ACs can originate de novo, from pre-existing ameloblastoma, or from odontogenic cysts. The majority of ACs develops de novo, although there are few instances of ameloblastoma undergoing malignant transformation. These tumors present in two variants: intraosseous and extraosseous/peripheral. The pathogenesis of AC is controversial, with multiple genes implicated in its malignant transformation. Mitochondrial apoptosis-inducing factors are believed to play a role in this transformation in ameloblastoma (4). Khojasteh et al. (2013) identified methylation of p16 in AC (5). Malignant odontogenic tumors exhibit upregulation of the coronin gene and downregulation of the STK19 (Serine/Threonine Kinase) gene (6). García-Muñoz et al. (2015) noted PITX2 expression in AC, which plays vital role in tumour proliferation, migration, and invasion (7). Positive expression of CD133 and Bmi-1 has been observed in odontogenic epithelial cells, ameloblastomas, and metastasizing ameloblastomas, with similar reactivity seen in ameloblastic carcinomas (8). Nodit et al. found that the frequency of allelic loss in ameloblastic carcinomas on chromosomes 1p, 3p, 9p, 17p and 10q is comparable to that observed in benign tumors. This suggests that distinct genetic mechanisms may be involved in driving malignant behavior (9). Although BRAF p.V600E their presence in ameloblastic carcinoma has been documented without established diagnostic significance (10) (11).

Ameloblastic carcinoma can occur across a wide range of age groups. AC mainly affects the elderly between 7 to 91 years (12) . There does not appear to be any sex preference. The posterior part of the mandible is the most frequently affected area. The occurrence of ameloblastic carcinoma in the maxilla appears to be less common compared to the mandible (13) (12).

It follows an aggressive clinical course, causing extensive local destruction (14). Clinically the most common signs and symptoms of AC include pain, swelling, dysphonia and trismus. Rapid growth of the tumour is another important clinical finding. Mental nerve parasthesia may also occur. In cases of maxillary ameloblastic carcinoma (AC), local invasion typically presents with a cheek mass, pain, fistula in the palate, involvement of the nasal cavity and parasthesia of the infraorbital nerve (15). The aggressiveness of ameloblastic carcinomas is evidenced by cortical plate perforation, extension into surrounding soft tissue, frequent recurrence, and metastasis, typically to the cervical lymph nodes.

In rare cases an AC may occur with malignancy associated hypercalcemia. This may be due to metabolic complication of malignancy. The two variants of malignancy associated hypercalcemia are Local osteolytic hypercalcemia and Humoral hypercalcemia of malignancy. Not more than four cases of malignancy associated hypercalcemia in AC have been reported (16).

Radiological examinations involve both plain X-rays and computed tomography scans. They reveal osteolytic lesions, which may appear unilocular or multilocular on radiographs. Screening for metastatic disease is recommended, especially in recurrent cases of typical ameloblastoma, malignant ameloblastoma, and ameloblastic carcinoma (5).

In general, it is difficult to differentiate between benign ameloblastoma and malignant ameloblastic carcinoma based solely on histopathological evaluation due to their highly similar histological features, especially in the early stages. However, the metastasizing variant is exceedingly rare and only approximately 30 cases have been documented in the literature. It has been suggested that repeated surgical excisions of recurrent ameloblastoma could be a contributing factor to the development of ameloblastic carcinoma, possibly serving as its primary cause (17).

A microscopic diagnosis of ameloblastic carcinoma necessitates a thorough understanding of odontogenesis and familiarity with the histological characteristics of ameloblastoma. Histologically, AC exhibits characteristics reminiscent of ameloblastoma, including cytologic atypia like hyperchromatism, increased nuclear cytoplasmic ratio, nuclear pleomorphism and increased mitotic activity with abnormal mitoses with 2 to 5 mitotic figure per high power field (18). Keratin pearl formation, individual cell keratinization, necrosis and dystrophic calcification have also been reported. AC consists of islands and cords of odontogenic epithelium with ameloblastomatous characteristics arranged in an infiltrative pattern within a fibrous connective tissue stroma. The epithelium exhibits a single outer layer of columnar or cuboidal ameloblastic cells, characterized by palisading and reversal of polarization. The central cells resemble stellate reticulum often presents in a less orderly pattern or condensed and hypercellular. Highly differentiated squamous cells may also be noted (19). The connective tissue stroma is usually fibrocellular with mild to moderate inflammatory cell infiltration, hemorrhage and hemosiderin pigment. The above mentioned microscopic features were coinciding with the present case.

Rarely, AC reveals clear cell differentiation where the clear cells may be observed within follicular epithelial islands. This variety may be misdiagnosed as salivary gland clear cell adenocarcinoma, or mucoepidermoid carcinoma or metastatic carcinoma like renal cell carcinoma. The presence of numerous clear cells, accounting for approximately 15% of the tumor cells, strongly indicates AC. Only a limited number of cases showcasing the clear cell variant of AC have been documented, and they appear to present with an aggressive clinical picture. Hall et al. observed that patients with clear cell variant of ameloblastic carcinoma experienced nearly twice as many recurrences as those in the non-clear cell group (2).

Research has identified use of phenotypic markers like Ki-67 proliferative index, BCL-2 proto-oncogene protein, p53 mutation, alpha-smooth muscle actin (α-SMA), and cytokeratins (CKs) has helped to assess the aggressive and malignant potential of these tumors (20) (21). Many proliferation markers like Ki-67, PCNA, and MCM proteins had been used to diagnose AC. Studies have shown that the expression and localization of Ki-67 vary dynamically throughout the cell cycle; it is less during G1 and early S-phase but increases significantly, peaking during mitosis. Ki-67 has proven to be a valuable marker for tumors to assess cell growth and tumor recurrence. Present case showed 50% proliferative index of Ki67. Bello et al., found that proliferative labeling index of Ki67 is higher in AC than that of ameloblastoma (21) and Casaroto et al. (2012) found that the mean labelling index was 42.45% (22). Other proliferative markers like PCNA and MCM can also be used. In 2013, Bologna-Molina et al. investigated PCNA and Ki-67 expression in AC, revealing a mean proliferation index of 48.7% with Ki-67 and 93.3% with PCNA, which was notably higher than that observed in AB (23). Cytokeratins (CKs) are keratin proteins of epithelial cells found in the intracytoplasmic cytoskeleton. Expression of CKs depends on the type of epithelial cell and its degree of differentiation. Numerous studies have shown the expression of various CKs (5, 7, 8, 13, 14, 18, and 19) in ameloblastomas. CK14 and CK19 are specifically predominant in certain odontogenic tumors,

including ameloblastoma. In our case, strong positivity for CK14 and CK19 indicated the lesion originated from odontogenic epithelium. CK7 positivity has also been observed in other odontogenic tumors such as odontoma, calcifying epithelial odontogenic tumor, and ameloblastic fibroma (24). Many studies have explored the expression of CK 7 in ameloblastic carcinoma. In our case, CK 7 showed no expression. Similarly studies by Yoon et al, Casaroto et al, Sancheti et al. Faizaan khan et al, also showed negative CK 7 expression (22) (25) (26) (27).

The potential list of differential diagnoses includes primary intra-alveolar epidermoid carcinoma, squamous cell carcinoma arising from the lining of an odontogenic cyst, calcifying epithelial odontogenic tumor, squamous odontogenic tumor, acanthomatous ameloblastoma, keratoameloblastoma, salivary gland neoplasms like pseudoadamantine adenocarcinoma, ductal carcinoma, high-grade mucoepidermoid carcinoma, and metastatic carcinoma to the jaws from sources such as the lung, breast, and gastrointestinal tract.

The preferred treatment is surgical resection. En bloc removal with a margin of normal bone measuring 1–2 cm is considered the safest surgical approach to ensure disease-free survival. This method has resulted in local recurrence rates of less than 15% (5). ACs can recur locally between 0.5 and 11 years after primary treatment. Maxillary AC noted to have unfavorable prognosis compared to mandible. Distant metastasis, which is often fatal, can occur as early as 4 months or as late as 12 years postoperatively. The lungs are the most common site for distant metastasis, followed by brain, liver and bones. Notably, distant metastasis can occur even without local or regional recurrence (25) (28). The prognosis of AC is entirely contingent upon its level of aggressiveness and metastatic potential.

3. CONCLUSION:

Given the limited number of cases of AC, there is a necessity for reporting and long-term evaluation of cases with comprehensive clinico-pathological correlation. This is essential for distinguishing it from more prevalent tumors, particularly ameloblastoma, and for developing treatment protocols, therefore histopathological examination of resected ameloblastoma is crucial to exclude any potential malignant transformation.

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