Correlation Between The Different Types Of Ameloblastoma And Immunohistochemical Analysis Of Tumor Markers

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By
Usama Saad Abd El Karim Hellal
BDS (2002)

Faculty of oral and dental medicine
Cairo University
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Supervisors

Prof. Dr. *Maha Shawky*

professor of oral & maxillofacial surgery
faculty of Oral and Dental Medicine
Cairo University.

Prof. Dr. *Naglaa Kholoussi*

professor of clinical pathology, chair of immunogenetic department
National Center of Researches

Dr. *Asmaa Ibrahim Salama*

Lecturer of Pathology National Cancer Institute
Cairo University

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List Of Abbreviations

AB----------Ameloblastoma

ABC --------- avidin biotin- complex

AC----------ameloblastic carcinoma

AMBN---------Ameloblastin protein

CDK---------- cyclin dependent kinase

ATM----------mutated in ataxia-telangiectasia

CD44v6-------cyclin dependent 44v6

c-myc----------nuclear transcription factor

E2F---------- transcription factor

EGFR----------epidermal growth factor receptor

h TERT---------telomerase reverse transcripase

ICAM-1------- intercellular adhesion molecule-1

Ki-67---------- protein expressed in all phases of cell cycle except G0 phase

LI ---------- label index

MAPK---------mitogen activated protein kinase

mdm2--------- murine double minutes 2

MK----------midkine

MMPs--------- matrix metalloproteinases

mRNA-------- messenger ribonucleic acid

MRI---------- magnetic resonance imaging

OPN---------- osteoporitin

p14 $^{(ARF)}$------protein product induced by a variety of oncogenic singals

pRb---------- retinoblastoma

Ras---------- Rat sarcoma

RFC----------replication factor c

SP1---------- stimulatory protein 1

TGF-beta---- transforming growth factor beta

TNFα --------tumor necrosis factor alpha

TRAIL------ TNF-related apoptosis-inducing ligand

UV---------- ultraviolet

VCAM-1-----vascular cell adhesion molecule -1

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Introduction

Ameloblastoma is a locally invasive neoplasm derived from odontogenic epithelium. It is the commonest one of odontogenic tumors; accounting for approximately 1% of all oral tumors. [(1)] It has received considerable attention over the years owing to its contradictory, paradoxic, and incongruent aspect of being a benign tumor arising from odontogenic epithelium but exhibiting an aggressive clinical behavior with high tendency for recurrence.[(2)] It occurs over a wide age range (10-92 years), with an average age of around 33 years with no gender predilection.[(3)] Approximately, 85% occur in the mandible with preledictionto the molar-ramus area.[(2)] The World Health Organization recognizes a range of histologic subtypes of ameloblastoma, such as follicular, plexiform, basaloid, acanthomatous, and granular variants, which have been well described in the literature. Despite this histologic diversity, different cellular patterns can coexist in the same lesion. [(4,5)]

It remains a subject of considerable interest, notably because of its locally invasive biological behavior, recurrence potential and the controversies regarding treatment modalities. Ameloblastomas are relatively resistant to chemotherapy or radiation therapy, thus, surgery is the most common treatment of this tumor. Treatment of ameloblastoma of the jaws has been either conservative or radical. The conservative approach includes enucleation or curettage and the radical approach includes resection (either segmental resection or marginal resection)**,** Because of the invasive nature of the growth, excision of normal tissue near the tumor margin is often required. Some researchers and clinicians

have considered ameloblastoma to be a low-grade malignant tumor that worth radical treatment.[2]

Immunohistochemical analysis of cell cycle regulatory proteins has been used to predict the biologic behavior of pathologic tissues which help determining the appropriate treatment modality, which has been always a matter of controversy .[6] The tumor suppressor protein p53 is up regulated in injured cells as p53 maintains genomic stability through the activation of multiple downstream pathways that regulate cell cycle arrest, cell repair and apoptosis.[7] Therefore, p53 is a tumor suppressor gene with key regulatory effects on both cell cycle and apoptosis. [8]

Proliferating cell nucler antigen (PCNA) is a nuclear nonhistone protein necessary for DNA synthesis, and is an accessory protein for DNA polymerase-alpha, which is elevated during the G1/S phase of the cell cycle. [9] PCNA expression may be used as a marker of cell proliferation because cells remain a longer time in the G1/S phase during proliferation. Also, this protein has an essential role in nucleic acid metabolism as a component of DNA replication and repair mechanism. An increase in PCNA levels may be induced by growth factors or as a result of DNA damage in the absence of cell cycle regulatory proteins. [10] PCNA-positive cells can be regarded as cells involved in the proliferating process. [11]

The expression of p53 and PCNA in neoplastic cells of different types of ameloblastomas by means of immunohistochemistry, using monoclonal antibodies against p53 and PCNA has helped to correlate between expression of p53 and PCNA with the clinical behavior and the histopathology in many other studies.[8,10]

Ameloblastoma

Odontogenic tumors are remarkable among oral lesions because of their clinical and histologic heterogeneity. This diversity reflects the complex development of dental structures because odontogenic tumors derive from aberrations in odontogensis. Ameloblastoma deserves special attention, not only because of its particular biologic behavior, exhibiting great infiltrative potential, high recurrence rate and capacity to metastasize, but also due to the relatively high frequency among odontogenic tumors [(12)]

Ameloblastoma is the most common odontogenic tumor originating from odontogenic epithelium, constituting 11–18% of all odontogenic tumors. [(13)] Although it is relatively rare. Ameloblastoma is a slowly growing, locally invasive, epithelial odontogenic tumor of the jaws with high rate of recurrence, even though the histology appears benign. [(14)]

The odontogenic origin of amloblastomas is derived from many similarities in the histological appearance of the tumor and a developing tooth organ. Possible origins of the neoplastic epithelium are discussed to be either disturbances of the developing enamel organ or epithelial lining of odontogenic cysts, particularly the dentigerous cyst, and odontomas or cell rests of the enamel organ, namely either remnants of dental lamina or remnants of Hertwigs root sheath (epithelial cell rests of Malassez) or the basal layer of the oral surface epithelium (epithelium of the jaws). [(12,15)]

Ameloblastoma is characterized by its histological resemblance to the enamel organ of developing tooth germ**,** yet enamel formation is not observed **.**[16-18] Ameloblastomas are locally destructive neoplasms with high rate of recurrence observed if the lesions are not entirely excised**.**[19] Few cases with malignant transformation and distant metastasis have been reported in the literature**.** [14, 20]

The cause of their invasiveness remains unknown. Several studies [16, 17] have been done in an attempt to clarify this phenomenon. Therefore, it is believed that this process involves the rupture of the basement membrane and the surrounding extracellular matrix with subsequent growth and proliferation of tumor cells. The invasive ability of ameloblastoma is also thought to be related to the release of biologically active molecules produced, such as matrix metalloproteinases (MMP), which in turn trigger mitogens to be released randomly, contributing to the cellular proliferation of ameloblastoma cells**.**

80% of ameloblastoma occur in mandible and the remaining 20% occur in maxilla. The main area of incidence is the mandible, and over two-thirds occur in the molar-ramus region**.** [1, 21] These lesions are rare in children and the greatest prevalence occurs in age range of 20 to 50 years**.** [17, 21] However, as they are characterized by slow-growth, their development probably initiate in childhood**.** [14]

Ameloblastoma appears as an aggressive odontogenic tumor, often asymptomatic and slow growing, with no evidence of swelling. It can sometimes cause symptoms such as swelling, dental malocclusion,

pain, mobility and resorption of teeth, paresthesia of the affected area and rarely ulceration of the mucosa**.** [1, 22]

The proliferating tumor may infiltrate the cancellous marrow spaces without causing bone destruction. It tends to expand the bone rather than perforate it. Occasionally patients allow an ameloblastoma to persist for many years without treatment and though the expansion may become extremely disfiguring and the tumor dose not break through the bone. But for unknown reasons some ameloblastomas manage to penetrate the bone and extend into the surrounding soft tissues**.** [12]

The appearance of septae on the radiograph usually represents differential resorption of the cortical plate by the tumor and not actual separation of tumor portions**.** [23] Because of its slow growth, recurrences of ameloblastoma generally present many years and even decades after primary surgery**.** [24] When treated inadequately, malignant development is a possibility**.** [1]

Concerning the different clinical variants of ameloblastoma**,** ameloblastoma is divided in to 3 clinicoradiologic groups: solid or multicystic, unicystic and peripheral ameloblastoma. The solid ameloblastoma is the most common form of the lesion (86%). It has a tendency to be more aggressive than the other types and has a higher incidence of recurrence**.** [25]

Unicystic ameloblastoma is defined as a cyst lined by ameloblastic epithelium with tall columnar basal cell layer, subnuclear vacuoles, reverse nuclear polarity and thin layer of edematous, degenerate