Study of epidermal growth factor receptor(EGFR) expression in benign and malignant Ameloblastoma Of The Jaws

by

Amna Othman Ali Elfeitouri

Supervisor

Prof. Azzam Ahmed Sultan

Prof. Ali Mahummed Elmurtadi

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Department of oral Pathology

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By: Amna Othman Ali Elfeitouri

This thesis was successfully defended and approved on **11.7.2020**

Supervisor

Prof. Azzam Ahmed Sultan

Sig. ……

Supervisor

Prof.Ali mohmmed Elmurtadi

Sig……..

DR……(Internal examiner)

Sig. ……

DR…… (External Examiner)

Sig. …….

(Dean of Faculty) **(Director of Graduate studies and training)**

DEDICATION

To my parents, my family and my country to all I dedicate this thesis.

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The researcher

Amna

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ABC	Avidin-Biotin Complex technique
Cyclin DI	On of the cell cycle proteins
DA	Desmoplastic Ameloblastoma
DAB	Diamino-Benzidine Soluation
EGFR	Epidermal Growth Factor Receptor
FNA	Fine Needle Aspiration
HGF	Hepatocyte Growth Factors
IHC	Immunohistochemical study
MDM2	Molecular Growth Factors
MRI	Magnetic Resonance Imaging
PCNA	Proliferating Cell Nuclear Antigen
P 53,P63and P73	Tumor protein 53,63,73
SMA	Solid multicystic ameloblastoma
UA	Unicystic Ameloblastoma
WHO	World Health Organization
AC	Ameloblastic carcinoma
CT	Compated tomography
MAPK	Mitogen – activated protein kinase
TWFA	Tumor nccrosis factory alpha
SD	Standard Deviation
SPSS	Statistic program

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ABSTRACT

Introduction: Ameloblastoma is a rare odontogenic neoplasm of the mandible and maxilla, with multiple histological variants, and high recurrence rates if improperly treated. It is a locally invasive neoplasm often associated with morbidity and facial deformities, showing increased epidermal growth factor receptor (EGFR) expression. EGFR stain location plays a vital role in assessing its proliferative potential, biological aggressiveness and treatment options.

This study was aimed to assess the clinic- histopathological features of the ameloblastoma cases and to study (Immunohistochemistry examination) the immune -expression of EGFR in ameloblastoma cases to clarify their role in the biological behavior of the benign and malignant ameloblastoma.

Materials and Methods: A descriptive case-series study of twenty-five patients diagnosed as ameloblastomas was conducted during the period from 1995 to 2010.The present study was undertaken in oral pathology laboratory at Faculty of Dentistry, University of Benghazi. The data were collected and reviewed from patients' charts. Clinical and epidemiological data were taken. Histopathological examination and Immunohistochemistry were done. The immune expression of EGFR reaction in ameloblastomas were positive or

negative reaction. Data collected and then analyzed by Statistical program (SPSS).

Results: The age of the subjects ranged from15 to 50 years with mean age 29.1 and SD 10.586 years. M:F ratio 1.5:1. More than half of cases of ameloblastomas mainly in right side of the mandible, while 44 % in left side of the mandible, and only 4% in both sides. Histopathological examination. Most cases were cystic 48 %, plexiform represents 32 % whereas, follicular and desmoplastic were seen in 16% and 4% of cases respectively. granular cell, acanthomatous and basal cell were not observed in the ameloblastoma. The ameloblastomas. cases (21) 86% were positively stained immune reactions to EGFR. The cells were observed mainly in combined of cytoplasmic and membranous followed by membranous, while nearly (only 4 lesions) represent 14% were negative staining.

Conclusions and Recommendations: The study concluded that most of ameloblastomas appear most commonly in the third to fifth decades. The majority of ameloblastomas indicate the biological behavior of the tumors as an aggressive because, most of tumors were solid and multicystic based on their histological classification, rather than benign also frequently invade locally and no metastasize was recorded .

The majority of ameloblastoma are positive for immune reaction to EGFR, about 9 cases combind cytoplasmic and membranous, 4 cases combined nuclear, cytoplasamic and membranous, 8 cases membranous. The distribution of EGFR expression in ameloblsatoma 48% focal reaction, 40% diffuse reaction, 12% negative reaction. The staining intensity of EGFR 6 cases strong positive staining, 11cases moderate positive staining, 4 cases weak staining, 4 cases negative reaction.

Chapter 1
Introduction

Introduction

The World Health Organization (WHO 1991) defined ameloblastoma as a benign but locally aggressive tumor with a high tendency to recur, consisting of proliferating odontogenic epithelium lying in a fibrous stroma [(1).]

Mc Clary et al. (2015) stated that Ameloblastoma is a rare odontogenic neoplasm of the mandible and maxilla, with multiple histological variants, and high recurrence rates if improperly treated [(2).]

Out of all the tumors and cysts of the jaws, ameloblastoma is cited to comprise about 1-3 % of them. Mandibular cases are more common than maxillary and demonstrate predilection for various regions of the mandible in ethnic groups [(2).] Ameloblastomas are the most common neoplasm of the jaw. They are usually first recognized between the ages of 30 and 50 years and rare in children and old people [(2,3).] Eighty percent occur in the mandible of these, 70% develop in the posterior molar region, and often involve the ramus [(2,3).] Ameloblastoma shows variable geographic prevalence being the most common benign odontogenic tumor in China and Africa, while it is the second most common in the United States and Canada [(2).]

African Americans have an overall five- fold increased risk of disease as compared to Caucasians [(2).] Global incidence has been estimated at 0.5 cases per million person years, and most cases are diagnosed in patients in the third and fifth decades of age [(4).]

The importance of this tumor lies in its common occurrence, locally invasive behavior which causes deformity and serious debilitation. They also demonstrate increased recurrence rate after surgery [(2)]. Almost always, an ameloblastoma manifests itself as a slow-growing, painless swelling, causing expansion of the cortical bone, perforation of the lingual and/or buccal bone along with infiltration of the surrounding soft tissue. There's frequently a lag

time in the investigation simply because of their slow-growing character and confusing nature [5].

Ameloblastoma is a slow growing and locally invasive odontogenic tumor with potentially destructive behavior and a high rate of recurrence. There is a possibility of transformation to a malignant tumor, although they are usually benign. However, they grow quickly and can change and destroy bone around them. Ameloblastoma develops in the jaw, often at the site of the third molar, and rarely involves tissue from the eye sockets or sinuses [6].

Growth is a highly coordinated process which is sustained by several growth factors and apoptotic factors. Any disturbance in this delicate balance leads to pathologies and genes that have such potential to produce tumors when mutated are known as oncogenes. Epidermal growth factor receptor (EGFR) is an important growth factor that is involved in several physiological processes is presently one of the most common genes in targeted cancer therapies [7].

Its potential as an oncogene target in squamous cell carcinomas of the head and neck epithelial tumors is gaining importance leading to revolutionization of cancer treatment modalities, its role in other head and neck epithelia like odontogenic epithelia remains vague and needs attention [7].

Epidermal growth factor receptor (EGFR) is transmembrane glycoprotein, the archetypal member of this family being the first to be sequenced as well as known to have tyrosine kinase activity [6].

Furthermore, ameloblastoma is a locally invasive neoplasm often associated with morbidity and facial deformities, showing increased EGFR expression [8]. EGFR with its ligand ,are cell signaling molecules involved in diverse cellular functions, that includes cell proliferation, differentiation motility, survival and development [8]. Nuclear Epidermal growth factor receptor occurs in ameloblastomas in association with Cyclin D1 expression, which is important in terms of tumor biology clarification and raises a concern about anti-EGFR treatment resistance in ameloblastomas [7].

The WHO classified the ameloblastoma in 2005 tumors classification as a group of tumors; each one of tumors of this group has its own clinical behavior and radiographic appearance. Local invasion and destruction of the adjacent structures are the source of risk in ameloblastoma. Nevertheless, a high rate of recurrence is reported after surgery [9] .

Immunohistochemical (IHC) study help to know the pathogenesis of the ameloblastoma [10]. Also by Immunohistochemical expression there is appositive correlation of EGFR in radicular cysts, dentigerous as well as Keratocystic odontogenic tumors [11].

The level of EGFR Expression by odontogenic cysts and rests is related to the presence of inflammation within adjacent connective tissue and that there is no detectable difference in receptor expression between developmental cysts and ameloblastoma [12]. Since ameloblastomas are EGFR-positive tumors, anti-EGFR agents could be considered to reduce the size of large tumors and to treat unresectable tumors that are in close proximity to vital structures [8,13].

Chapter 2

REVIEW OF LITERATURE

REVIEW OF LITERATURE

2.1 History:

Ameloblastoma, is derived from the English word "amel" which means enamel and the Greek word "blastos" which means the germ [14]. It arises from the epithelium of the dental lamina, and it is characterized by its local aggressive behavior and a high recurrence rate. Ameloblastoma was first described in 1827 by Cusack [15]. In 1885, Malassez introduced the name "adamantinoma," which is presently used to illustrate a rare form of bone cancer described by Fisher in 1913 [16].

It was first detailed and described by Falkson in 1879. The term ameloblastoma was coined by Ivey and Churchill in 1930, [17,18] a currently accepted term. It is considered as a true neoplasm as the name implies it mimics the cells of the enamel-forming organ. It was described by Robinson in 1937, as a benign tumor that is "usually unicentric, nonfunctional, intermittent in growth, anatomically benign and clinically persistent." The World Health Organization (WHO) (1991) defined ameloblastoma as a benign but locally aggressive tumor with a high tendency to recur, consisting of proliferating odontogenic epithelium lying in a fibrous stroma [1].

2.2 Epidemiology:

The annual incidence rates per million for ameloblastomas are 1.96, 1.20, 0.18 and 0.44 for black males, black females, white males and white females respectively. Ameloblastomas account for about one percent of all oral tumors and about 18% of odontogenic tumors. Men and women tend to be equally affected, although women tend to be 4 years younger than men when tumors first occur, and tumors appear to be larger in females [19].

In the continents of Africa and Asia, this tumor is seen very commonly, and, in the USA, it is the second most common odontogenic tumor [3].

Ameloblastoma shows variable geographic prevalence being the most common benign odontogenic tumor in China and Africa while it is the second most common in the United States and Canada [2]. African Americans have an overall fivefold increased risk of disease as compared to Caucasians; global incidence has been estimated at 0.5 cases per million person years [2].

2.3 Clinical features:

The most common presentation for ameloblastoma is a painless swelling of the mandible or maxilla [20], though in a series of 60 patients, up to 35 % had their lesion identified as an incidental finding on imaging [21]. Pain is uncommon but can occur because of hemorrhage, especially following a fine needle aspiration (FNA) [22]. Pain with rapid growth may represent the rare malignant ameloblastoma. Tooth displacement and root resorption are infrequent but have been reported in up to 25 % of desmoplastic ameloblastomas [23]. Paresthesias are uncommon with rare reported cases of perineural invasion Up to 80 % of ameloblastoma cases occur in the mandible, with a predilection for the posterior mandibular region [24].

Rare cases have been reported as primary to the sinonasal cavities. Ameloblastoma can be associated with unerupted third molar teeth, particularly in the unicystic type [25].

However, they grow quickly and can change and destroy bone around them. Ameloblastoma develops in the jaw, often at the site of the third molar, and rarely involves tissue from the eye sockets or sinuses. From literature ameloblastoma is the most frequent benign tumor of the odontogenic tumors that develops in the jaw. Nevertheless, a high rate of recurrence is reported after surgery [8].

2.4 Malignant ameloblastoma and ameloblastomic carcinoma:

The ameloblastoma is an odontogenic tumour of the jaws, arising from dental embryonic remnants possibly from the epithelial lining of an odontogenic cyst;

dental lamina or enamel organ; stratified squamous epithelium of the oral cavity; or displaced epithelial remnants [26].

Ameloblastoma is a benign but locally aggressive odontogenic epithelial neoplasm,which presents as a slowly growing painless swelling of the jaws. It constitutes about 1–3% of all jaw tumours and cysts [27]. It occurs more commonly in blacks than in whites [28].

The maxillomandibular ratio of ameloblastoma is 5:1 with more susceptibility in the mandible, and the most common site of occurrence is the mandibular molar region [24, 29]. More than 50% of recurrence occurs within the first 5 years after primary surgery [24].

The malignant form of ameloblastoma has been controversial for many years. The term ‘malignant ameloblastoma’ implies that lesions metastasize despite their benign histology. The term ameloblastic carcinoma (AC) is reserved for an ameloblastoma with a malignant morphologic appearance, regardless of the presence of metastasis [30].

Malignant variants of the ameloblastoma are exceptionally rare and may arise de novo or from transformation of a long-standing primarily benign lesion which has undergone several surgical excision [31].

Ameloblastic carcinoma (AC) is an extremely rare, aggressive malignant epithelial odontogenic tumor and has a poor prognosis. Two thirds of these tumors arise from the mandible while one third originates in the maxilla [32]. The most common symptom is a rapidly progressing painful swelling [30]. It may also present as a cystic lesion with benign clinical features or as a large tissue mass with ulceration, significant bone resorption and tooth mobility [26].

The terms malignant ameloblastoma and ameloblastic carcinoma have been used interchangeably for these variants in the past, it is now generally agreed

that malignant ameloblastoma tends to metastasizes in spite of the benign histology in both the primary and the metastatic lesion [33,34] while ameloblastic carcinoma exhibit histologic features of both ameloblastoma and carcinoma [32 , 34].The tumour may metastasize and histologic features of malignancy may be found in either the primary tumour, the metastases or both [30, 35].

Both etiology of this rare carcinoma and the question whether this type of carcinoma originates from an ameloblastomas or represents a separate entity are still controversial [36]. There are difference of the opinion regarding treatment of ACs; however, wide surgical excision with or without radiotherapy is the most commonly used treatment modality [33].

Ameloblastic carcinoma occurs in a wide range of age groups. There is no apparent sex predilection. The most commonly involved area is the posterior portion of the mandible [34]. Involvement of the maxilla by ameloblastic carcinoma seems to be less frequent than that of the mandible [33,34]. The most common sign is swelling, although others include associated pain, rapid growth, trismus and dysphonia [33].

Radiological investigations include both the plain X-ray and computerized axial tomography. They appear as osteolytic processes, exhibiting a unilocular or multilocular appearance on radiograph. Screening for metastatic disease should be done, especially in recurrent cases of typical ameloblastoma, malignant ameloblastoma, and ameloblastic carcinoma [37]. Radiographic appearance of the AC is consistent with that of an ameloblastoma except for the presence of some focal radiopacities, apparently reflecting dystrophic calcifications. These histologic and radiologic features are not generally seen in conventional ameloblastomas. Clinically, these carcinomas are more aggressive than typical ameloblastomas. Perforation of the cortical plate, extension into surrounding soft tissue, numerous recurrent lesions and metastasis, usually to cervical lymph nodes, can be associated with ameloblastic carcinomas [34].

The main differential diagnosis for this tumor was squamous cell carcinoma, in particular, the basaloid variant. In this case the features that distinguished the AC from squamous cell carcinoma included the jigsaw puzzle-type nesting of the tumor cells, the presence of stellate reticulum, and the distinctive cystic degeneration of the nests. The diagnosis of craniopharyngioma can be also considered in the differential diagnosis, primarily because of its well-known similarities to odontogenic neoplasia and partially because of its location in the cranial base. However, these possibilities are ruled out because the findings were characteristic of AC [30].

The most common site for a distant metastasis is the lung, followed by bone, liver, and brain [28, 38]. Distant metastasis can occur in the absence of a local or regional recurrence [28]. ACs can recur locally 0.5–11 years after definitive therapy [38]. Distant metastasis is usually fatal and may appear as early as 4 months or as late as 12 years postoperatively [38].

2.5 Diagnosis:

Preoperative diagnostic evaluation includes imaging and possible biopsy. Ameloblastomas originate within bone, apart from the peripheral subtype which arise in the gingiva or buccal mucosa, and thus are often detected incidentally on dental X-rays (pantomography) or plain films; X-rays usually show a lytic lesion with scalloped margins, resorption of tooth roots, and impacted molars (unicystic) [39,40]. The classic ‘‘soap bubble’’ appearance is seen with the most common ameloblastoma, the multilocular/solid type [40].

Although sometimes adequate for complete evaluation, plain X-rays lack sensitivity and specificity for the extent of bone and soft tissue invasion. Computed tomography (CT) is the most useful diagnostic imaging modality, typically demonstrating well defined radiolucent uni/multilocular expansile lesions [21]. CT is also useful for the evaluation of cortical destruction (revealing

a window for biopsy) and soft tissue extension, identifying the full extent of the tumor to support surgical planning [41, 42]. MRI provides potentially more complete information than CT about soft tissue extension and marrow extension beyond the lytic bone cavity [43]. MRI is particularly useful for ameloblastomas arising from the maxilla, as it helps to characterize extension to the orbit, paranasal sinuses, and skull base. MRI should be considered in desmoplastic ameloblastomas because they have poorly defined soft tissue borders and are often misdiagnosed as a fibro-osseous lesion [44]. PET-CT is generally reserved for metastatic ameloblastoma, where it may aid with staging of the distant metastasis.

Imaging findings are characteristic but not pathognomonic, and the diagnosis is classically established by histology. Biopsy may be helpful prior to treatment to avoid unnecessary operations on lesions of alternative etiology that should be alternatively treated or simply observed, such as osteomyelitis, cystic fibrous dysplasia, giant cell tumor, ossifying fibroma, multiple myeloma, and rare sarcomas. Biopsy also allows for proper preoperative staging in malignant ameloblastomas [45].

Furthermore, over-treatment of benign dentigerous cysts that cannot be differentiated from some unicystic ameloblastomas must be avoided; these cannot be diagnosed on FNA and need open biopsy in the form of curettage. A biopsy should be done at the start of the case to sort this out. Maxillary ameloblastomas often present with involvement of adjacent soft tissue, resembling adenocarcinomas and squamous cell carcinomas. Fine needle aspiration can be acquired via a window of cortical erosion as identified by imaging or from the dental socket. Incisional biopsy can provide a more accurate diagnosis but requires disruption of the mucosa, which will ultimately need to be removed at surgery. Peripheral ameloblastomas are not covered by bone and can be biopsied without difficulty [2].

2.6 Management:

Surgical resection is the treatment of choice. En bloc removal with 1–2 cm of normal bone margin is the safest surgical modality to ensure disease-free survival. This method has resulted in local recurrence rates of less than 15% [37]. Historically, the extent of resection has been controversial, comprising of two surgical options: ‘‘conservative’’ vs. ‘‘radical’’. The former involves enucleation/curettage of the bony cavity, while the latter involves a radical operation with appropriate margins. Advantages of enucleation include the fact that it is an outpatient procedure able to be performed by many different service providers (Oral Surgeons and ENT), since it requires no reconstruction. Historical data on simple enucleation demonstrate recurrence rates 60–90 %, however, and this treatment modality is currently believed to play no role in the management of multicystic ameloblastomas [21, 22, 46, 47– 52].

The ‘‘radical’’ surgical option is the current standard of care for ameloblastoma and includes en bloc resection with 1–2 cm bone margins [53, 54 – 57] and immediate bone reconstruction to help with speech and swallowing [54,58–60]. The bony margin is defined as the distance away from the radiographic margin predicted to be disease free and oncologically safe to perform osteotomies.

Chemotherapy as primary treatment does not appear indicated. Results of such treatment for non-metastatic disease have been poor [61]. However, in the setting of metastatic disease, Ramadas et al. [62] found the use of cisplatin, adriamycin, and cyclophosphamide to be beneficial. Methotrexate and leucovorin has been also used [37].

There is controversy regarding radiotherapy of Ameloblastoma, and it is considered radioresistant tumour [63]. There is no well-documented evidence

concerning the true radioresponsiveness of these tumors. Authors have doubt on its effectiveness [64, 65].

2.7 Prognosis:

The major prognostic factor is the clinical course of the disease which include its aggressiveness, local destruction, and distant metastatic spread preferentially through hematologic route if neglected [66]. In addition, this relatively high risk of distant metastasis differs with that of squamous cell carcinomas that spread rather by the lymphatic way [66]. Distant metastasis is usually fatal and may appear as early as 4 months or as late as 12 years postoperatively [38].

However, once metastases occurred, the median survival have been reported to be 2 years [67]. It is also important to note that distant metastasis can occur in the absence of a local or regional recurrence [28]. The location of ameloblastic carcinoma also contributes to its prognosis as maxillary ameloblastic carcinoma have an unfavorable prognosis as compared to that located in the mandible [68]. In the Nigerian experience, recurrence ranged from 6 to 96 months after the initial surgery. Six patients died overall with three deaths within 3 years after the first surgery [69]. One patient died about 8 years after the initial surgery [69].

Many factors were related with the prognosis of ameloblastoma. Some scholars1[46,70] believed that a radical surgery should be used for the multicystic ameloblastoma to prevent the recurrence. From the pathological aspect, the follicular ameloblastomas were thought to have a higher recurrence rate than plexiform or unicystic [71] Takahashi et al.[72] found that ameloblastoma in children was mainly the plexiform type, and conservative treatment could be accepted as the initial treatment. Due to lack of the cortical plates, ameloblastoma in maxilla was thought to spread readily into the adjacent vital regions and suggested to be treated by extensive resection [71,47].

It is valid to use radiographs to estimate the growth rate of focal osseous lesions in clinical practice. Ueno et al.[50] reported that biological behavior of the ameloblastoma was related to the radiographic appearance, and the multilocular type of ameloblastoma had a poor prognosis. The radiographic boundary of ameloblastoma is another useful parameter inevaluating the growth rate ofthe tumor. Kramer 1963 [(73)] stated that, while ameloblastomas invaded the intertrabecular spaces of cancellous bone, they do not invade compact bone, although they may erode it.

Ameloblastoma which has a well-defined edge with sclerosis is thought to grow slowly, and the normal bone has a strong reaction to form the sclerosis edge, which acts like compact bone to resist the invasion of the tumor, even if the size of the lesion is comparably large. So the tumor is confined and the prognosis is good. On the contrary, if the tumor's radiographic boundary is not sclerotized, the tumor was thought to be a little more aggressive and the prognosis is not so optimistic. Ameloblastomas with ill-defined boundary are thought to have the most aggressive behavior than others, which should be treated by the radical surgery because of the higher recurrent probability[(73)].

2.8 Pathogenesis:

While the molecular pathogenesis of ameloblastoma was largely unknown prior to 2014, there was mounting evidence suggesting that activation of the mitogen-activated protein kinase (MAPK) pathway plays a prominent role. Several studies demonstrated activation of components of the MAPK pathway in an ameloblastoma cell line (AM-1) under various circumstances, including stimulation with tumor necrosis factor alpha (TNF α) [(74)] and fibroblast growth factors 7 and 10 [(75).] In addition, transgenic mice expressing v-Ha-Ras under the zeta-globin promoter were shown to develop odontogenic tumors resembling ameloblastoma [(76).]

Ameloblasts are of ectodermal origin and derived from oral epithelium. The cells are only present during tooth development that deposit tooth enamel, which forms the outer surface of the crown. Ameloblasts become functional only after odontoblasts form the primary layer of dentin (the layer beneath enamel). The cells eventually become part of the enamel epithelium and eventually undergo apoptosis (cell death) before or after tooth eruption. There exist deposits of these cells in the structures in and around the tooth, termed cell rests of Malessez and cell rests of Serres. Current thought is that ameloblastomas can arise from either the cells mentioned above or other cells of ectodermal origin, such as those associated with the enamel organ. Approximately 80% occur in the mandible and the other 20% in the maxilla [77].

Ameloblastomas and odontogenic cysts like keratocystic odontogenic tumor and dentigerous cysts are often derived from the epithelial remnants and follicles and this suggests that early intervention of removing the impacted teeth and associated follicles can reduce pathologies to a certain extent. It is also hypothesized that ameloblastomas can be reduced in size and recurrence can be prevented by using anti- EGFR agents as several studies on ameloblastoma molecular pathways suggest that several downstream markers show increased EGFR immunohistochemical expression and mutations [78].

Immunohistochemical reactivity for EGFR downstream markers like BRAF, K-Ras, MEK1, Raf1, and ERK1/2 have been identified in both normal odontogenic epithelium as well in odontogenic tumors [79].

2.9 Histopathology:

Ameloblastoma is a rare, benign, slow-growing but locally invasive neoplasm of odontogenic origin involving the mandible (80 %) and maxilla; conservative treatment results in a high recurrence rate. The neoplasm was first described by Cusack in 1827 [15]. Etymologically, the name derives from the old French word ‘‘amel,’’ which means enamel, and the Greek word ‘‘blastos,’’ meaning germ or bud. Over time, this tumor has been referred to by many different names including ‘‘cystosarcoma,’’ ‘‘adamantine epithelioma,’’ ‘‘adamantinoma,’’ and finally ‘‘ameloblastoma’’ [80, 81].

Histopathologically, ameloblastoma resembles normal odontogenic/ enamel epithelium and ectomesenchyme. Odontogenesis consists of chronographic and reciprocal interactions between the ectomesenchymal cells, which are derived from the neural crest, and the oral cavity lining epithelium [82]. Ameloblastic epithelium has been hypothesized to arise from (1) cells from the rests of enamel organ, but also from (2) cells of the sheet of Hertwig’s or epithelial cell rest of Malassez, (3) epithelial boundary of an odontogenic cyst, particularly a dentigerous cyst, (4) basal cells of the oral mucosa, (5) heterotopic epithelial from other parts of the body, perhaps pituitary [83, 84].

2.9.1 Classification and subtypes:

There are three main clinical subtypes of ameloblastoma: unicystic, multicystic, peripheral [85]. The peripheral subtype composes 2% of all ameloblastomas. Of all ameloblastomas in younger patients, unicystic ameloblastomas represent 6% of the cases [85]. A fourth subtype, malignant, has been considered by some oncologic specialists, however, this form of the tumor is rare and may be simply a manifestation of one of the three main subtypes. Ameloblastoma also occurs in long bones, and another variant is Craniopharyngioma (Rathke's pouch tumour, pituitary ameloblastomaral

airways making it impossible to breathe without oropharyngeal histopathology (85).

In the 2005 World Health Organization classification the benign ameloblastoma is divided into:

1) solid/multicystic.

2) extra-osseous/peripheral.

3) desmoplastic.

4) unicystic (9).

The solid/multicystic ameloblastoma can histopathological be divided into a follicular and a plexiform type the follicular type can be further subdivided into a spindle cell type, an acanthomatous type, a granular type and a basal cell type (9). The plexiform type contains basal cells arranged in anastomosing strands with an inconspicuous stellate reticulum. The stroma is usually delicate, often with cyst like degeneration (9).

The unicystic ameloblastoma represents an ameloblastoma variant that on gross examination, and not based on the appearance on the radiograph, presents as a cyst. Two histopathological variants are recognized, being the luminal variant and the mural variant (9). The peripheral type shows the histopathogical cell types and patterns as seen in the solid / multicystic type (18). In the desmoplastic type the stromal component dominates, compressing the odontogenic epithelial components.

Moreover, WHO classification for ameloblastomas includes the four subtypes whereas the solid/multicystic is the most common type comprising 91 % of the ameloblastomas in the largest series (9). This is followed by the unicystic type 6 %, the extraosseous ameloblastoma 2% and the desmoplastic type 1% (9,86). The most aggressive clinical /pathologic association is seen in the solid/multicystic type, which is associated with the highest recurrence rate of up to 90 % with operations such as enucleation and curettage conservative (86). The unicystic

type is the most benign and is further classified into intraluminal and intramural subtypes [86].

The intraluminal unicystic subtype does not exhibit invasion of the supporting connective tissue does not exhibit invasion of the supporting connective tissue has the lower recurrence rate of the two subtypes and may be the only histology amenable to conservative surgical treatment [9,86].

Currently in 2017 the classification has been simplified and narrowed to ameloblastoma, unicystic ameloblastoma and extraosseous/peripheral types. The adjective "solid/multicystic" for the conventional ameloblastoma was dropped because it has no biologic significance and can lead to confusion with unicystic ameloblastoma. Desmoplastic ameloblastoma will be reclassified as a histologic subtype and not a clinicopathologic entity.

Despite its unique clinical and sometimes radiographic features, it behaves like any conventional ameloblastoma. Odontoameloblastoma was included in the classification in 2005. The association of ameloblastoma with odontoma is well established and accepted, but the consensus group did not think it justified being separated as an entity. There is no evidence that these tumors begin as odonto-ameloblastomas or recur as odonto-ameloblastomas; they recur as ameloblastomas.They believe that these ameloblastomas arise in an odontoma from primitive ectoderm just as they arise from primitive ectoderm involved in odontogenesis. Accordingly, the association is discussed under ameloblastoma and is more accurately described as an ameloblastoma arising in an odontoma, not odontoameloblastoma [87].

2.9.2 Solid / Multicystic Ameloblastoma:

The solid or multicystic ameloblastoma is a benign epithelial odontogenic tumor of the jaws. It is slow growing locally aggressive and accounts for about 10% of all odontogenic tumors in the jaw. Solid multicystic ameloblastoma (SMA) occur as growths arising from remnants of odontogenic epithelium, exclusively from rests of the dental lamina. SMAs may also arise as

a result of neoplastic changes in the lining or wall of a non-neoplastic odontogenic cyst, in particular dentigerous and odontogenic keratocysts [9,86].

2.9.3 Unicystic Ameloblastoma:

Unicystic ameloblastoma (UA) represents an ameloblastoma variant, presenting as a cyst that show clinical and radiologic characteristics of an odontogenic cyst. In histological examination shows a typical ameloblastomatous epithelium lining part of the cyst cavity, with or without luminal and/or mural tumor proliferation. In 1977, Robinson and Martinez first used the term "UA, but it was also named in the second edition of the international histological classification of odontogenic tumors by the WHO as cystogenic ameloblastoma. 5-15% of all ameloblastomas are of the unicystic type, the unicystic type is the most benign and is further classified into intraluminal and intramural subtypes [9,86].

A review of 193 cases of unicystic ameloblastoma (UA) in study of Philipsen and Reichart [85], revealed that radiographically, the uniocular pattern is more common than the muliocular, especially in cases associated with both impaction, also reported between 50% and 80% of cases are associated with tooth impaction, furthermore, histologically, the minimum criterion for diagnosing a lesion as UA in the demonstration of a single cystic sac lined by odontogenic (ameloblastoma) epithelium often seen only in focal areas [85].

2.9.4 Plexiform ameloblastoma:

The term plexiform refers to the appearance of anastomosing islands of odontogenic epithelium in contrast to a follicular pattern [88].

Histologically, ameloblastoma is characterized by the proliferation of epithelial cells arranged in a collagenous fibrous connective tissue stroma of conjunctive vascular tissue in locally invading structures that resemble the enamel organ at different stages of differentiation, histopathological features showed anastomosing sheets and cords of odontogenic epithelium. The epithelium displayed a stellate, reticulum-type appearance, arranged as a

tangled network of anastomosing strands, enclosing cysts of various sizes. It was predominantly composed of epithelium arranged as a tangled network of anastomosing strands, enclosing cysts of various sizes, suggestive of plexiform ameloblastoma, plexiform ameloblastoma is associated with recurrence rate nearly 16.7 % while follicular ameloblastoma is characterized by higher recurrence rate nearly 29.5% [88, 89].

2.9.5 Follicular ameloblastoma:

The follicular type can be further subdivided into a spindle cell type, an acanthomatous type, a granular type and a basal cell type. Follicular ameloblastoma showing peripheral palisading and central reticulum stellate pattern), also the follicular pattern stimulates the developing dental follicle and the enamel organ by arranging the epithelial cells to resemble stellate reticulum. The follicular ameloblastoma consists of discrete organ and with varying quantity of connective tissue stroma. The follicular ameloblastoma characterized by higher recurrence rate [86].

2.9.6 Acanthomatous ameloblastoma:

The acanthomatous variant is extremely rare. One-third of ameloblastomas are plexiform one-third are follicular. Other variants such as acanthomatous occur in older patients. The acanthomatous ameloblastoma represents a subtype of solid multicystic ameloblastoma with specific microscopic features [90,91].

2.9.7 Granular cell ameloblastoma:

Granular cell ameloblastoma is a rare condition, It is a less common histological subtype of ameloblastoma [92,93]. Accounting for 3.5% of all ameloblastoma cases that shows marked transformation in the cytoplasm of tumor cells, which are usually stellate reticulum like cells [93].

The transformed cells possess very coarse, granular, eosinophilic cytoplasm. The “granular change” is thought to be due to a dysfunctional status

of neoplastic cells, and the pathogenesis of this tumor seems to be age-related. Ultra-structural, histochemical, and immunohistochemical studies have revealed that cytoplasmic granularity is caused by overload; however the mechanism involved remains poorly understood ([93).]

2.9.8 Basal cell ameloblastoma:

Basal cell ameloblastoma occurs predominantly in the fourth decade, mean age being 57.3 years. Most of the published cases report that basal cell variant presented predominantly in males, but we present two cases in females. The posterior mandible has a definite predilection for this variant although cases have been reported in the maxilla. [(94).]

The basal cell ameloblastoma is a rare variant of ameloblastoma with very few cases reported until date [(95).] The most common presenting symptom in basal cell variant was swelling followed by ulceration of the oral mucosa as seen in two of the three cases reported. The radiologic appearance of this variant is most commonly multilocular– multicystic pattern [(94).] Histologic tumor reveals multiple follicles, strands, and cords of odontogenic epithelium in connective tissue stroma that is minimal. The peripheral cells of follicles exhibit hyperplasia and are basaloid in appearance. The central portion in most of the follicles shows cystic degeneration [(94).]

2.9.9 Desmoplastic ameloblastomas:

First reported by Eversole et al in 1984 and was recently included in the WHO's classification of head and neck tumors. This tumor is characterized by an unusual histomorphology, including extensive stromal collagenization or desmoplasia, leading to the proposed term ameloblastoma with pronounced desmoplasia or DA [(1,85).] Desmoplastic ameloblastomas often occur in the anterior or premolar regions of the mandible or maxilla. Ameloblastic carcinomas also favor the mandible (2/3) over the maxilla, maxillary ameloblastomas also mostly occur in the posterior molar region [(2,24,90).]

2.9.10 Peripheral Ameloblastoma:

The peripheral ameloblastoma (PA) is defined as an ameloblastoma that is confined to the gingival or alveolar mucosa. It infiltrates the surrounding tissues, mostly the gingival connective tissue, but it does not involve the underlying bone [86,96]. PA arises from remnants of the dental lamina, the so-called "glands of Serres," odontogenic remnants of the vestibular lamina, pluripotent cells in the basal cell layer of the mucosal epithelium and pluripotent cells from minor salivary glands [86,96].

The PA is an exophytic growth restricted to the soft tissues overlying the tooth-bearing areas of the jaws. The mandibular premolar region accounts the commonest site. Histologically same patterns are as in solid type, with a common type being acanthomatous. Differential includes peripheral reactive lesions such as pyogenic granuloma, papilloma, fibroma, peripheral giant-cell granuloma, peripheral odontogenic fibroma, peripheral-ossifying fibroma, Baden's odontogenic gingival epithelial hamartoma, and basal cell carcinoma [85].

2.10 Epidermal growth factor receptor (EGFR):

EGFR is the archetypal member of this family being the first to be sequenced as well as known to have tyrosine kinase activity. EGFR structure consists of one polypeptide chain consisting of 1186 amino acid residues weighing 170 kDa with three domains; the extracellular, transmembrane and the intracellular domains containing tyrosine kinase enzyme [97]. The extracellular domain is the ligand bind domain and mainly binds epidermal growth factor (EGF) and other similar ligands like TGF-β, hepatocyte growth factor (HGF) and neuregulins [98]. On binding of the specific ligand they form a homo- or heterodimer complex, following which there is internalization of the

receptor-ligand complex resulting in auto phosphorylation of the tyrosine which activates an internal cascade of signaling pathways that mediate various cellular functions like determination of cell lineage, cellular proliferation, cell homeostasis, organ morphogenesis, cellular motility and cell survival [99].

In study of localization of epidermal growth factor receptor in ameloblastomas by Pereir et al 2015, revealed that ameloblastoma is a locally invasive neoplasm often associated with morbidity and facial deformities, showing increased epidermal growth factor receptor expression [7].

Inhibition of EGFR was suggested as a treatment option for a subset of ameloblastomas, however, there are resistance mechanisms that impair anti-EGFR therapies. One important resistance mechanism for EGFR-inhibition is the EGFR nuclear localization, which activates genes responsible for its mitogenic effects, such as Cyclin D1[7].

A study done by Bhavna C and his colleagues (2015), reported that the immunohistochemical examination of 35 pericoronal follicles removed from patients with asymptomatic impacted tooth extraction. The follicles predominantly showed intense staining pattern and location of EGFR positivity in most epithelium and rests were combined both cytoplasmic and membrane positivity [6]. The findings reemphasize the inherent proliferative potential present in follicles and their role in formation of odontogenic tumors like ameloblastomas in long term impacted teeth [8].

The potential of EGFR as a treatment target in odontogenic tumors also remains plausible [6]. In addition, EGFR has been shown an importance in the genesis and behavior of some types of this tumor like solid multilocular ameloblastoma. Ki-67 is a molecule that can be easily detected in proliferating cells in order to gain an understanding of the rate at which the cells within a tumor are growing [8].

Much immunohistochemical (IHC) research has been conducted in the last two decades in an attempt to elucidate the etiologic factors and treatment

modalities for this tumor. Epidermal growth factor (EGF), a member of the ErbB family, is a transmembrane glycoprotein that stimulates cell growth, proliferation, and differentiation by binding to its epidermal growth factor receptor while Ki-67 is a molecule that can be easily detected in growing cells in order to gain an understanding of the rate at which the cells within a tumor are growing [8].

Furthermore, evaluation of Ki-67 status together with conventional histological evaluation can help in providing more information about the biologic behavior of the tumor, while EGFR could be a target of an expanding class of anticancer therapies. Since ameloblastomas are EGFR-positive tumors, anti-EGFR agents could be considered to reduce the size of large tumors and to treat unresectable tumors that are in close proximity to vital structures [8]. Identification of proliferating activities in tumors may be useful to predict their biological behavior. Ki-67 protein is a nuclear non-histone protein which is required for maintaining the cell cycle. Ki-67 is expressed by proliferating cells in all phases of the active cell cycle (G1, S, G2 and M phase) but is absent in resting (G0) cells that's why Ki-67 has been used to determine the proliferation rate of ameloblastomas [8].

EGFR is responsible in the ameloblastic differentiation and plays a role in amelogenesis. From literature it was noted that the peripheral tall columnar cells and pre-ameloblasts had a membranous staining pattern. These findings suggest that understanding EGFR stain location plays a vital role in assessing its proliferative potential, biological aggressiveness and treatment options [78, 100].

Signaling pathway such as growth factors like fibroblast growth factor play a pivotal role in the pathogenesis of solid type of ameloblastoma. Proteins mainly bone morphogenic protein ameloblast in enamel matrix proteins calretinin, syndecan-1 and matrix metalloproteinases also play an important contribution in the etiopathogenesis. Tumor suppressor genes p53, p63 and p73

bring about molecular changes in the pathogenesis of ameloblastoma. p53 plays an important role in the differentiation and proliferation of odontogenic epithelial cells [86,96]. Matrix metalloproteinases, triggers mitogens to be released, leading to the proliferation of ameloblastoma cells [86,96]. It is also hypothesized that ameloblastomas can be reduced in size and recurrence, can be prevented by using anti- EGFR agents as several studies on ameloblastoma molecular pathways suggest that several downstream markers a show increased EGFR immunohistochemical expression and mutations [78]. Immunohistochemical reactivity for EGFR downstream markers like BRAF, K-Ras, MEK1, Raf1, and ERK1/2 have been identified in both normal odontogenic epithelium as well in odontogenic tumors [79].

Likewise, there are microscopic similarities recorded that, the nuclear immune a study of the role of Epidermal growth factor receptor in odontogenic epithelium and development of odontogenic lesions, the study also noted that pericoronal follicles (PFs) showed predominantly intense combined and cytoplasmic staining patterns, suggestive of an inherent potential for proliferation in dental follicles [6]. The areas of squamous metaplasia showed a consistent membrane EGFR expression, which highlights the role of EGFR in squamous differentiation and may be related to early pathological changes in dental follicles [6]. EGFR remains one of the most targeted oncogenes with several anti-EGFR agents like cetuximab, gefitinib, erlotinib in monotherapy and combination being used in several carcinomas like head and neck squamous cell carcinoma colorectal, non-small cell lung cancer and pancreas [101,102].

Chapter 3
Aim of Study

Aim of Study

1. To assess the clinic- histopathological features of the ameloblastoma cases.
2. To study (Immunohistochemistry examination) the immune-expression of Epidermal growth factor receptor (EGFR) in ameloblastoma cases to clarify their role in the biological behavior of the benign and malignant ameloblastoma.

Chapter 4
Materials and Methods

MATERIALSAND METHODS

4.1 Study design study period and sample size:

A descriptive case-series study was conducted during the period from Jan 1995 to December 2010 from archive of oral pathology in the Faculty of Dentistry university of Benghazi. A convenient sample of twenty-five patients (n = 25) diagnosed as ameloblastomas. During the 15 years these 25 cases were the only cases that perfectly match clinically, radiologically and histopathologically criteria of the ameloblastomas.

The period of this study was nine months, which was distributed as follow:

Three months for reviewing literatures on ameloblastomas.
Three months for collect the data and histopathology stained by haematoxylin, eosin stain.

Three months for collection data and analysis.

4.2 Study setting:

The present study was undertaken in oral pathology laboratory at Faculty of Dentistry University of Benghazi (previously known as Al-Arab Medical University). The immunohistochemical (IHC) investigation, stained by immune marker in the oral pathology department Zagazig University at Cairo – Egypt to study immune reactions. The data were collected and reviewed from patients' charts. Clinical and epidemiological data such as age, gender, and nationality, site of the ameloblastoma and if it is benign or malignant.

All cases were reviewed histologically, and four-micron thick sections were cut and stained with haematoxylin and eosin (H and E) to confirm the diagnosis and to study histopatological features according to Kramer, Pindborg and shear.[1]

For examination of Immunohistopathological reaction of the epidermal growth factor receptor (EGRF), Avidin –Biotin complex (ABC) Technique were used in the following way.

4.4 Immunohistochemistry (IHC):

Formalin- fixed, paraffin-embedded tissue blocks sliced at 4-micron thickness and mounted on coated glass-slides. Sections were deparaffinized and immersed in methanol with 0.3% hydrogen peroxide.

For antigen retrival, they heated in an autoclave (121C, 2 atm) in 0.01 M citrate buffer (PH 6.0) for 10 min, after treatment with normal serum ; the sections incubated with primary antibodies at 4C overnight . The applied antibodies were anti-epidermal growth receptor. The standard labeled streptavidin-biotin-peroxidase complex method according to Goncalves e t al 2012[103], was preformed to bind the primary antibody by a p histofine SAB-PO Kit (Nichirei, Tokyo , Japan) reaction was visualized by immersing the section in 0.03% diamino-benzidine (DAB) solution containing 2Mm hydrogen peroxide 3 -5 min.

The section counterstained with mayers hematoxylin and examined by light microscope Immunoreactions color is brown when stained by diamino-benzidine (DAB) solution.

Immunohistochemical reactions were carried out using streptavidin- biotin immunoperxidase system with EGFR**.**

4.4.1 Interpretation and evaluation of immunostaining:

Evaluation of EGFR immunostaining: Both cytoplasmic, membranous and nuclear staining of epithelium was considered positive for EGFR.

EGFR immuno positivity was graded semi quantitatively as:

Score 1- Weak (light immunostaining involving less than 10% of the epithelium).

Score 2 – Moderate (light to moderate immunostaining involving 10 to 50%).

Score 3- (moderate – to strong immunostaining involving more than 50%) these classifications according to Inoue et al 2005.

The immune expression of EGFR reaction in Ameloblastoma were positive or negative reaction.

Normal, postive and negative controls were staind at the same staining setting with the studies cases.

Postive control: normal testicular tissue and human breast carcinoma for testing EGFR were used.

Negative control: Were employed using antibody dilutuent in buffer instead of primary antibody.

4.5 Statistical methods:

Statistical analysis on study results was per-formed by the application of the statistical package social science soft ware version 17 (SPSS Inc, Chicago, Il, USA). Data collected and then analyzed and expressed as frequency distributions and then computed in percentages a in tables and figures. Simple statistical parameters such as mean, standard deviation, minimum and maximum were done.

Chapter 5

Results

RESULTS

The total number of cases diagnosed as ameloblastoma were 25. Males (M) were more than females (F), M = 15 and F=10 cases with M: F ratio 1.5:1 (figure 1). The age of the subjects ranged from 15 to 50 years with mean age 29 and Standard Deviation (SD) was 10.586 years (figure 2) (table 1).

Most of the cases were Libyan 22 casas (88%), whereas the non-Libyan were 3 cases (12%), (one from Chad and two from Sudan), twenty-two patients were resident in Benghazi (88%), while 3 (12%) cases of the patients were from out- side Benghazi (one from Derna, one from Ajdabia and one from Sabha, (figure 3).

More than half of the cases of ameloblastoma were mainly in the right side of the mandible (13, 52%). The posterior part of the mandible was the most favored site of twenty-two cases whereas only three cases out of the 25 cases were in the anterior region. The result records of ameloblastomas in the mandible showed that most cases were at the angle, while the remaining were in the area of the molars, ascending ramus or in the premolar region, no cases reported in the Maxilla.

The histopathological examination showed that when the cases of ameloblastoma stained with Haematoxylin and Eosin (H and E) stain, the majority of cases 12 were Cystic type (48 %) (figure 8, 9), while Plexiform cases were about 8 (32 %)(figure 10), whereas Follicular cases were 4 (16%) (figure 11), only one case (4%) was Desmoplastic (figure 12), Granular cell, Acanthomatous and Basal cell ameloblastoms were not observed. Also, with (H and E) stains, we found 21 (84%) of cases were benign and only 4 (16%) of the cases from total number were diagnosed as malignant ameloblastoma (figure 4,13). The majority of the ameloblastoma cases were solid multicystic, 16 cases (64.71%) were solid multicystic and the minority 9 cases were unicystic (35.29 %), (figure 5).

The immunohistochemistry examination indicated according to our study, that the majority of ameloblastoma cases 21 (86.36%) were positively stained to EGFR, while only 4 cases (13.64%) had a negative immune reaction to EGFR, (figure 6, table 3). In 21 cases of positively stained ameloblastoma there was 9 cases (42.8%), the expression was combined between cytoplasmic and membranous (figure18,19), while 8 cases (38.1%) were only observed in the membranous (figure15,16), also only 4 cases (19%) were the expression was combined in (nuclear, cytoplasmic and membranous) (figure 20), (table 4).

The ameloblastomas staining was graded between weak, moderate, strong. In this study there was one case of the plexiform and 3 cases of the cystic type of ameloblastoma were weak reaction (no staining or light immunostaining) (figure 23, 24), the vast majority of the 21 cases were 5 cystic ameloblastoma, 3 cases of the follicular and 3 cases of the plexiform with moderate reaction light to moderate immunostaining) (figure 14, 20, 22).

It was recorded that 11 cases (48%) of the ameloblastomas were focal positive reaction (figure 7, 17) and 10 cases (40%) were diffuse reactions (figure 7, 18, 20, 21), while only 4 cases (12%) of ameloblastoma were negative reactions, (figure 25, 27).

According to our study, 15 cases were basally immune stained reaction (figure 17, 24) and about 6 cases were combined basal and supra basal (figure 19, 20, 21). While, 2 cases of follicular ameloblastoma 2 cases of plexiform, 1 case cystic and 1 case desmoplastic type showed strong reaction with EGFR (moderate – to strong immunostaining) (figure 17, 18, 19, 21), (table 5).

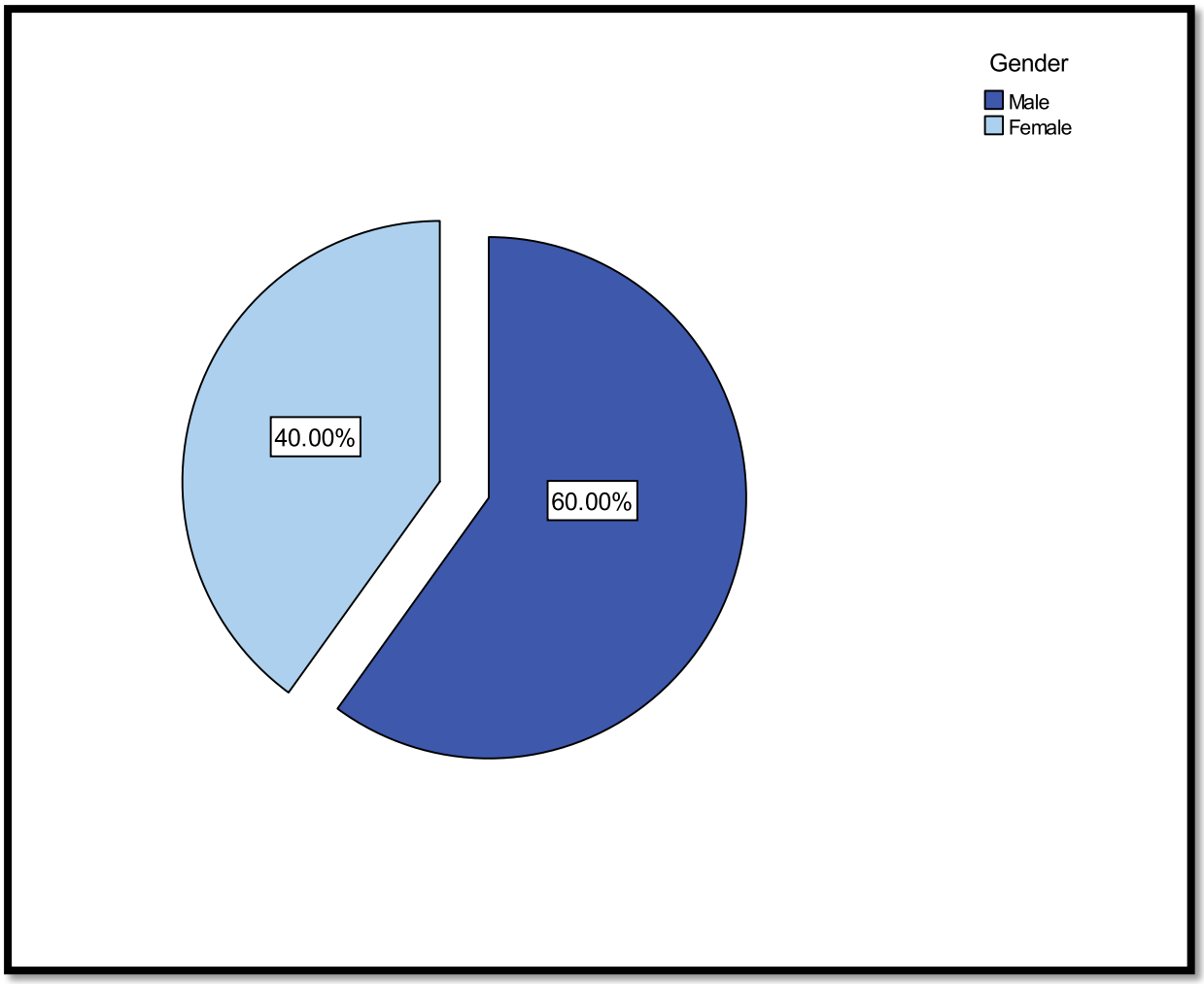
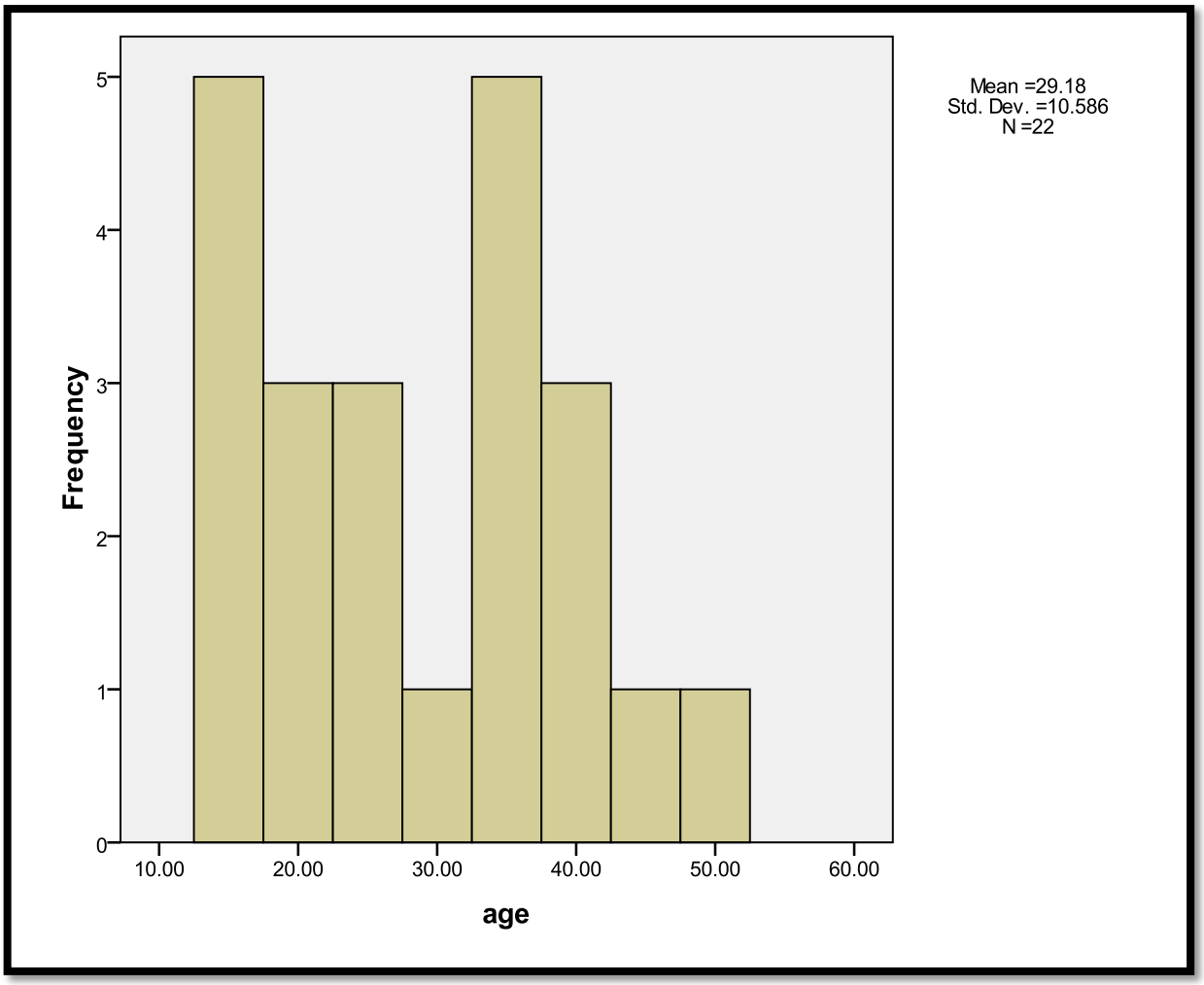


Figure (1): Distribution of the cases of ameloblastoma according to gender.

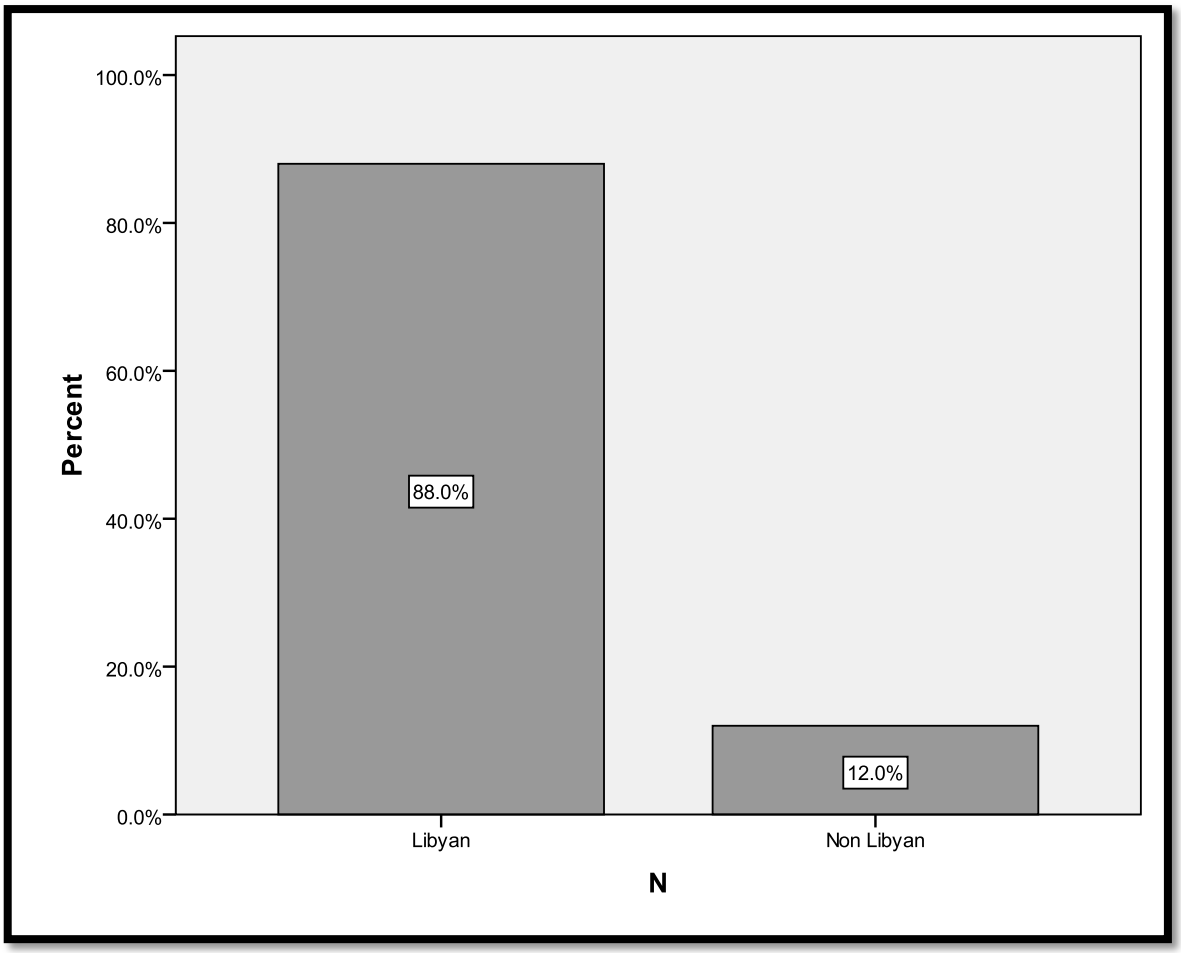


N (number), SD (standard deviation).

Figure (2): Distribution of the cases of ameloblastoma according to age.

Table (1): Descriptive Statistics of age distribution of twenty-five patients of ameloblastoma in Benghazi.

Total	Minimum Age	Maximum Age	Mean Age	Std. Deviation
25	15 years	50 years	29.1	10.586



N (nationality).

Figure (3): Distribution of the cases of ameloblastoma according to nationality.

Table (2): Frequency of different subtypes of ameloblastoma (Histopathological features of twenty-five cases).

Histopathology	Number of cases	Percent %
Follicular	4	16 %
Plexiform	8	32 %
Cystic	12	48 %
Granular cell	0	0 %
Acanthomatous	0	0 %
Desmoplastic	1	4 %
Basal cell	0	0 %
Total	25	100 %

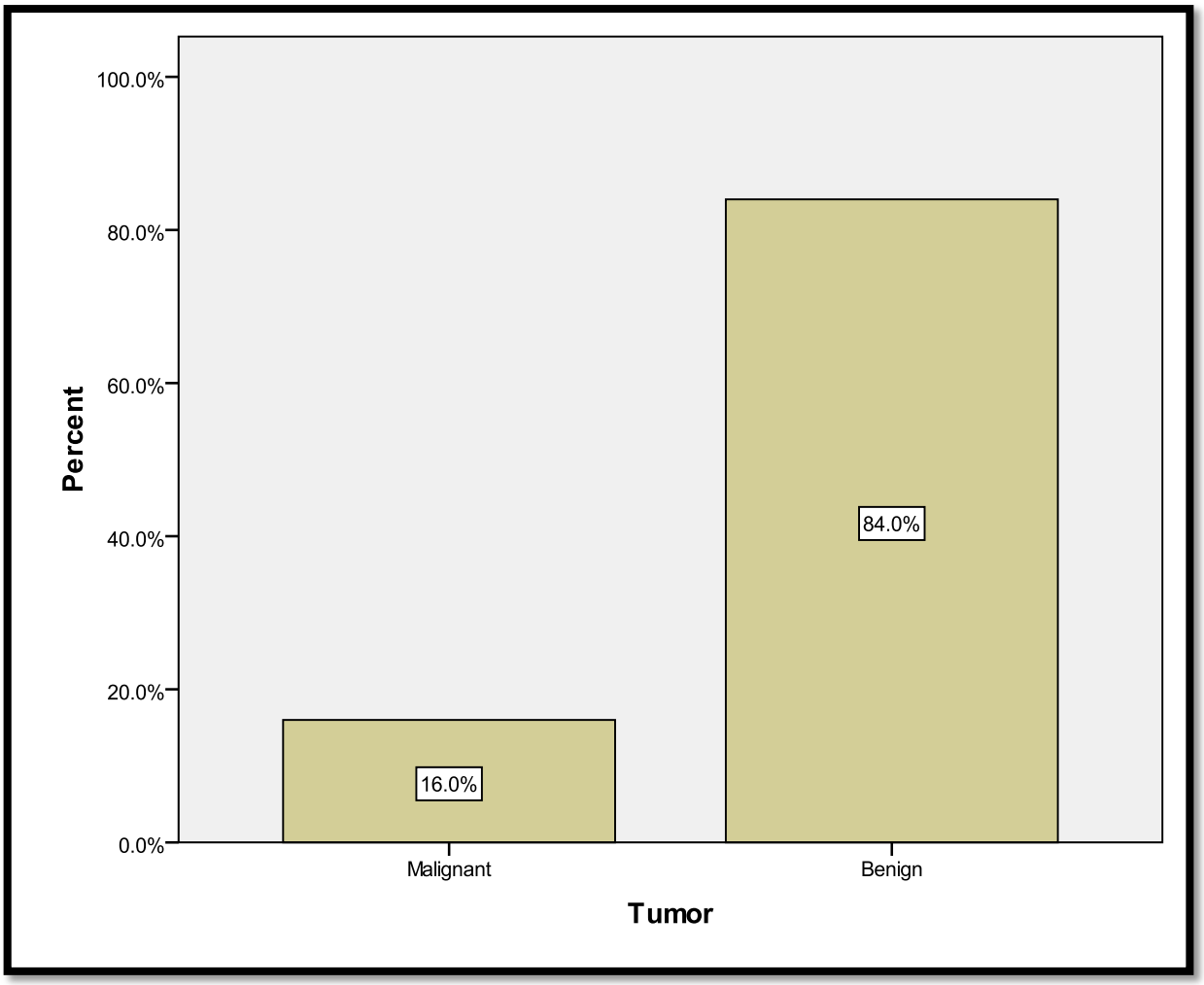


Figure (4): Distribution of the cases of ameloblastoma according to benign and malignant.

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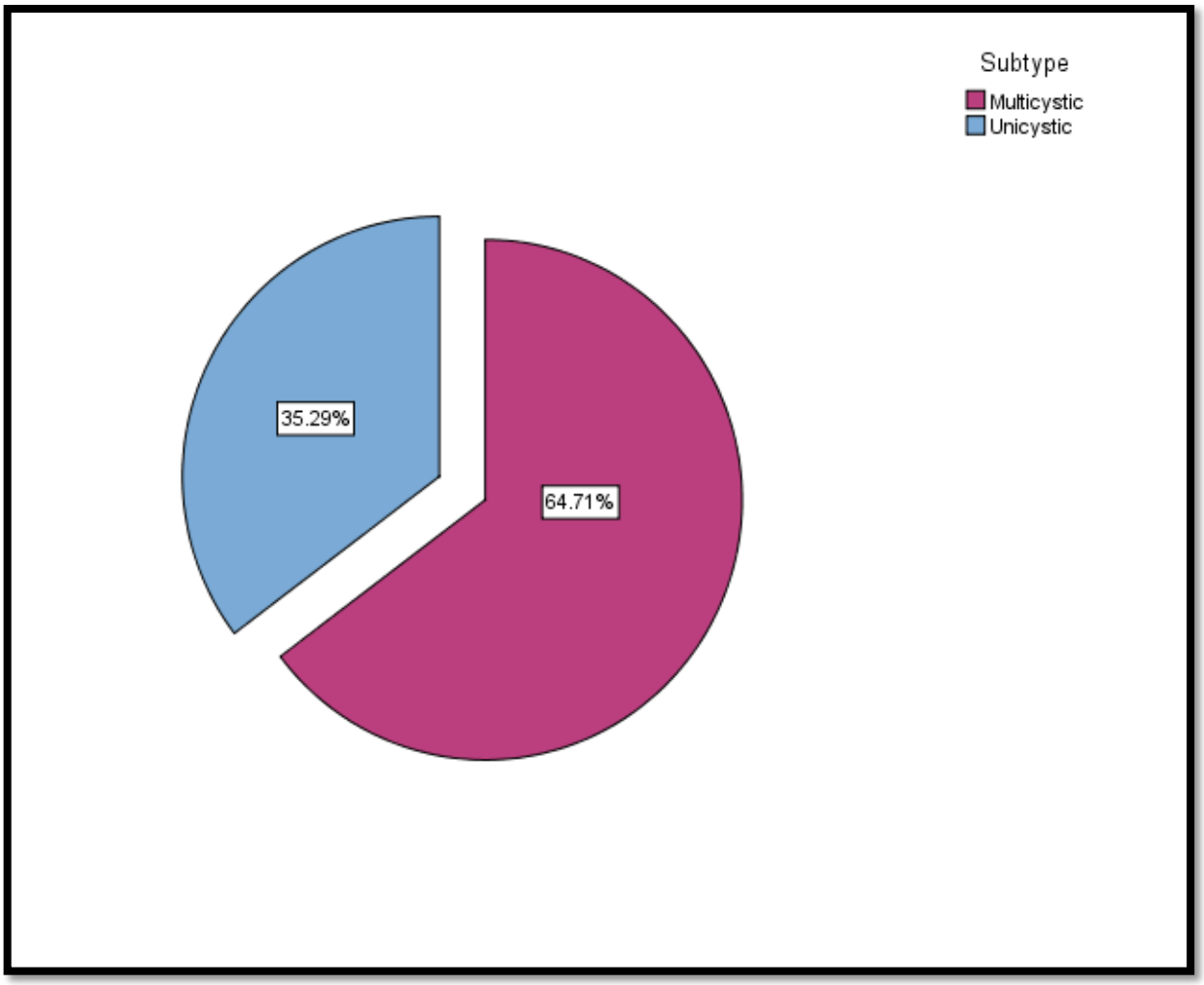

Figure (5): A biological subtype of a unicystic or multicystic ameloblastoma.

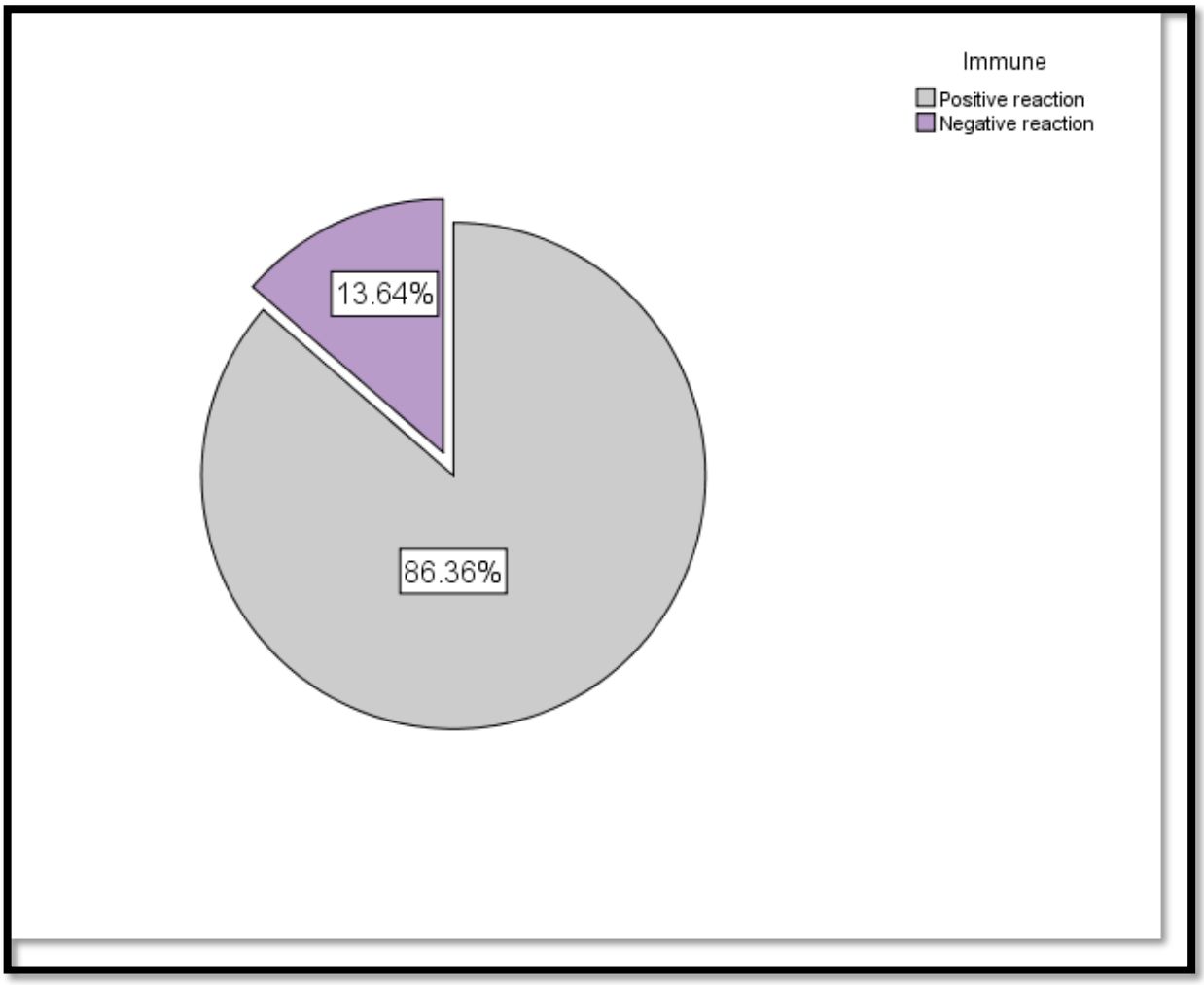

Figure (6). The expression of immuno reaction to EGFR in ameloblastoma

Table (3): The immune expression of epidermal growth factor receptor (EGFR) in ameloblastomas.

Reactions	No.	Percent %
Positive reaction	21	86 %
Negative reaction	4	14 %
Total of cases	25	100 %

Table (4): Immunohistopathplogical features expression of epidermal growth factor receptor (EGFR) in ameloblastoma.

(EGFR)	Number	Percentage
Combined (cytoplasmic and membranous)	9	42.9 %
Combined (Nuclear, cytoplasmic and membranous)	4	19 %
Nuclear	0	0 %
Membranous	8	38.1 %
Total Positive	21	100 %

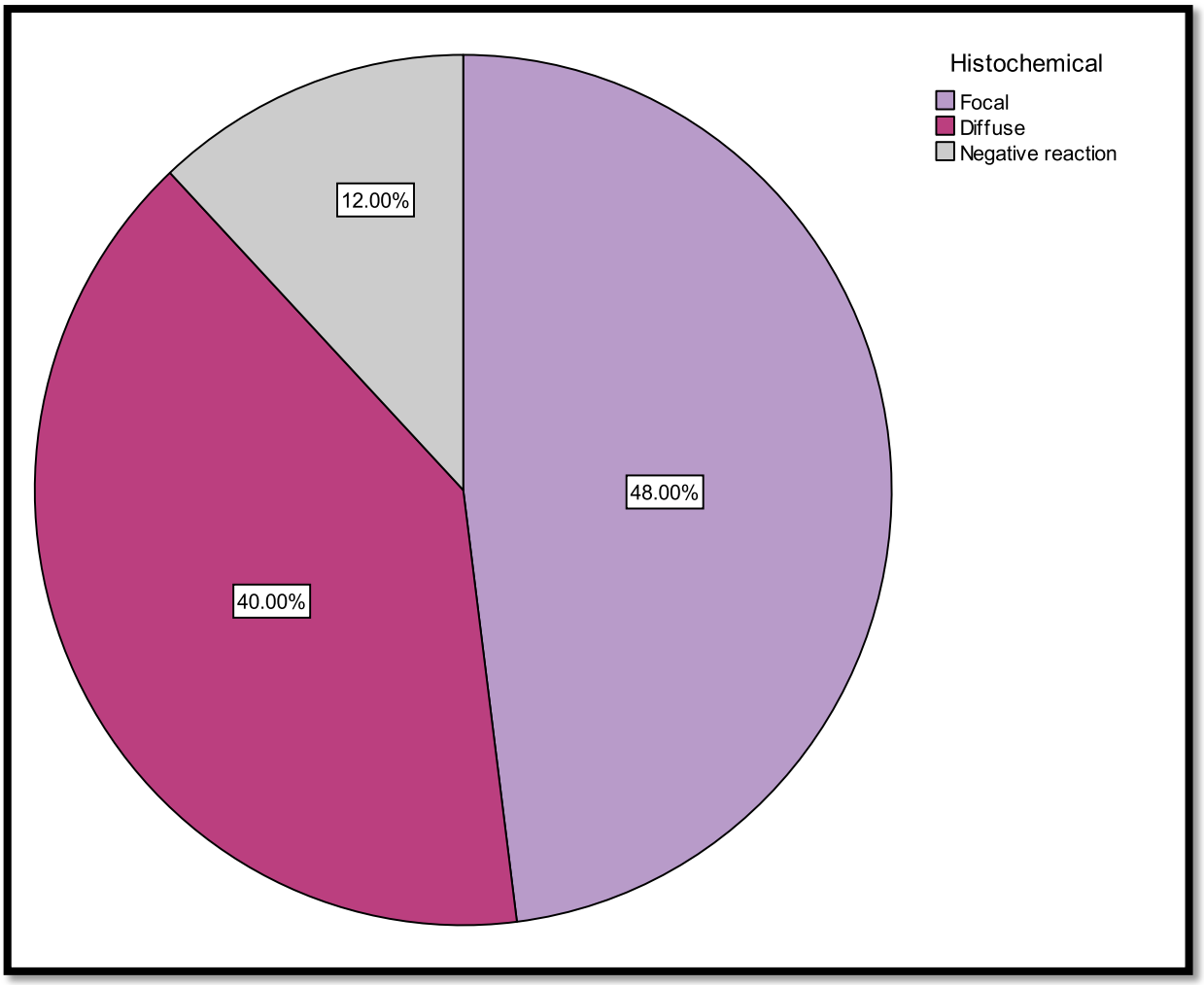

Figure (7): Distribution of the EGFR expression in ameloblastoma according to diffuse or focal reactions,

Table (5): Positive Staining intensity of immun reactions.

Histopathology	Weak	Moderate	Strong
Follicular	0	3	2
Plexiform	1	3	2
Cystic	3	5	1
Desmoplastic	0	0	1
Total lesions = 21			

Histopathological examination of ameloblastomas by Hematoxylin and Eosin (H and E)

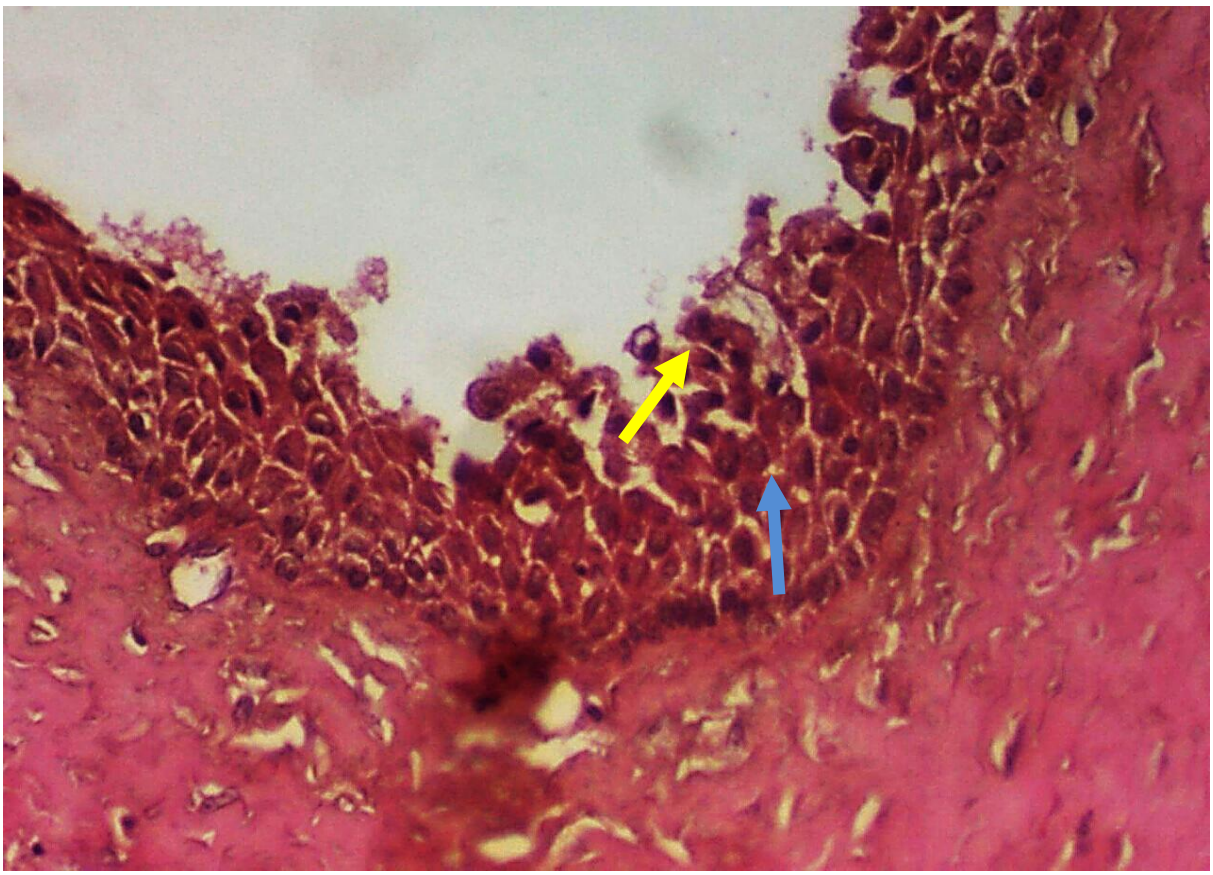

Figure (8) Photomicrograph of histopathological section of cystic ameloblastomoma showing yellow and blue arrow a cystic space filled with few layers of ameloblastomic cells (Hematoxylin and Eosin ×400)

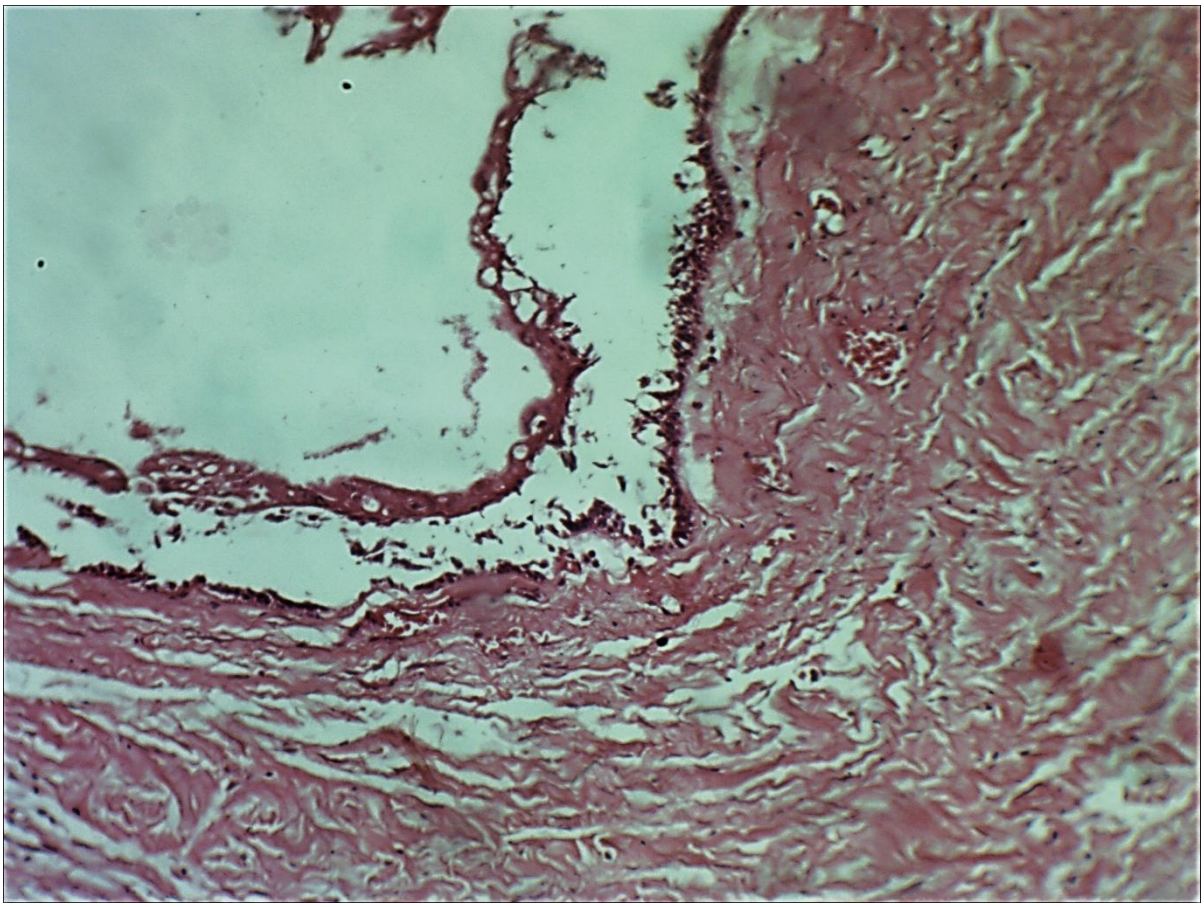

Figure (9) Photomicrograph of histopathological section of cystic ameloblastoma (Hematoxylin and Eosin ×100).

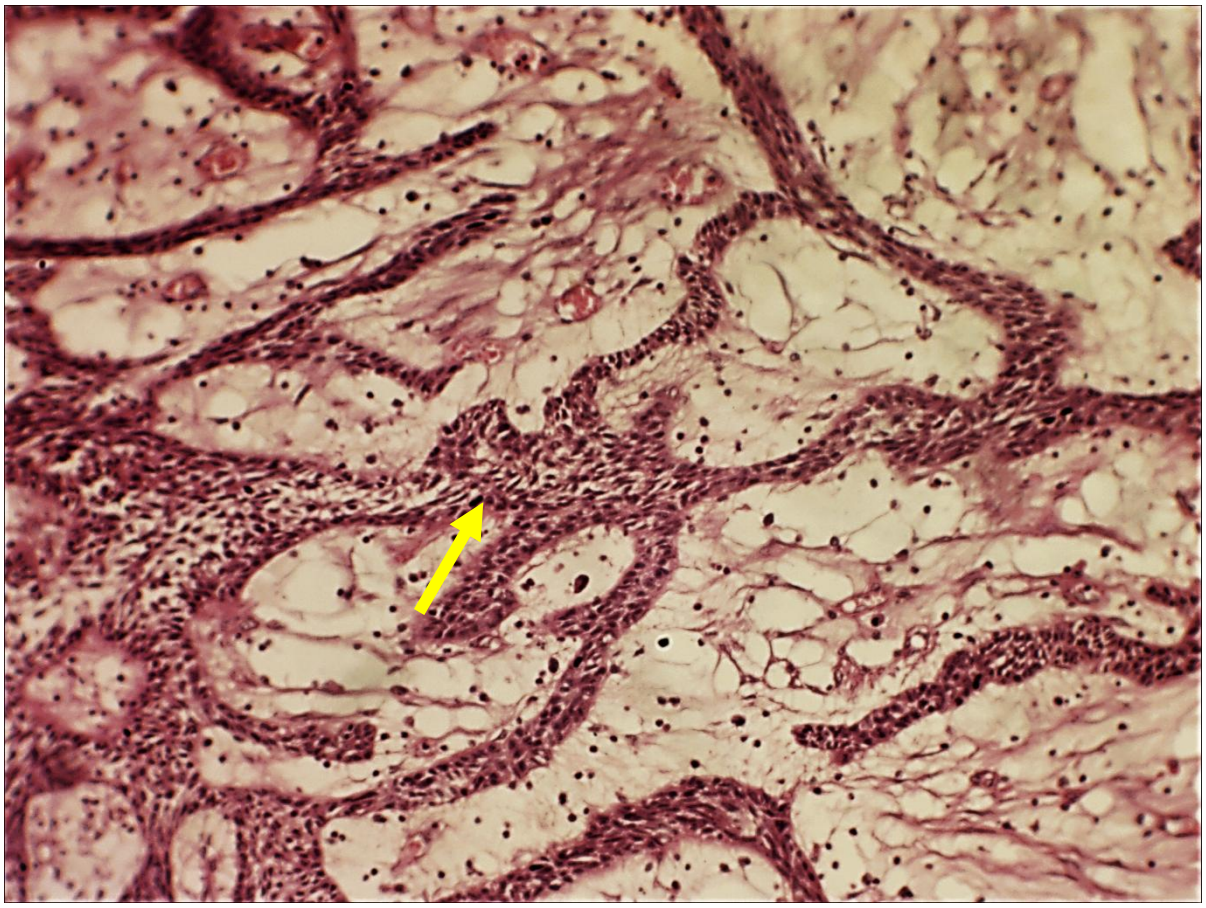

Figure (10) Photomicrograph of a histopathological section of plexiform ameloblastoma yellow arrow (Hematoxylin and Eosin ×100).

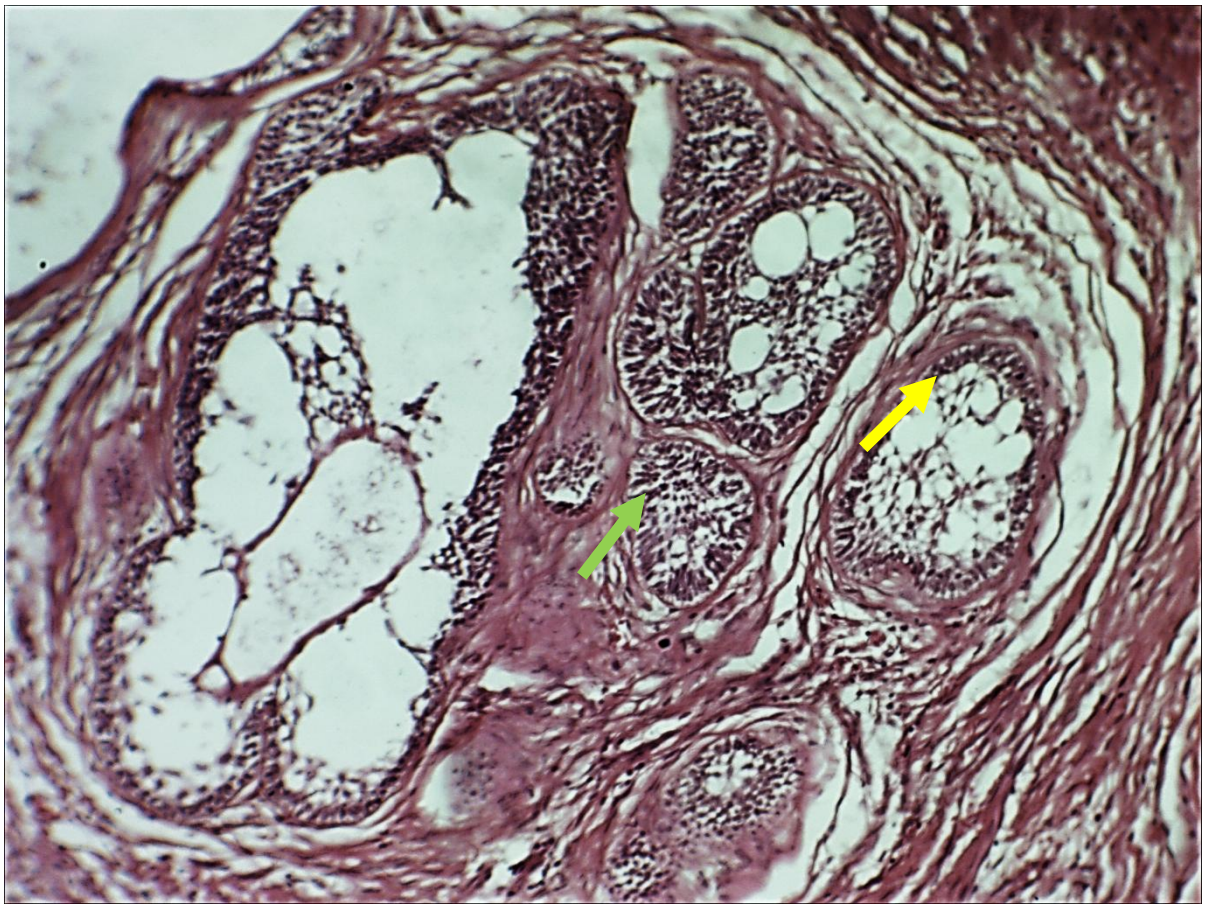

Figure (11) Photomicrograph of a histopathological section of follicular ameloblastoma showing odontogenic epithelium which in some places exhibit hyper chromatic layer of palisaded basal cells (green arrow) and layers resemble satellite reticulum (yellow arrow) surrounded by fibrous connective tissue. (Hematoxylin and Eosin ×100).

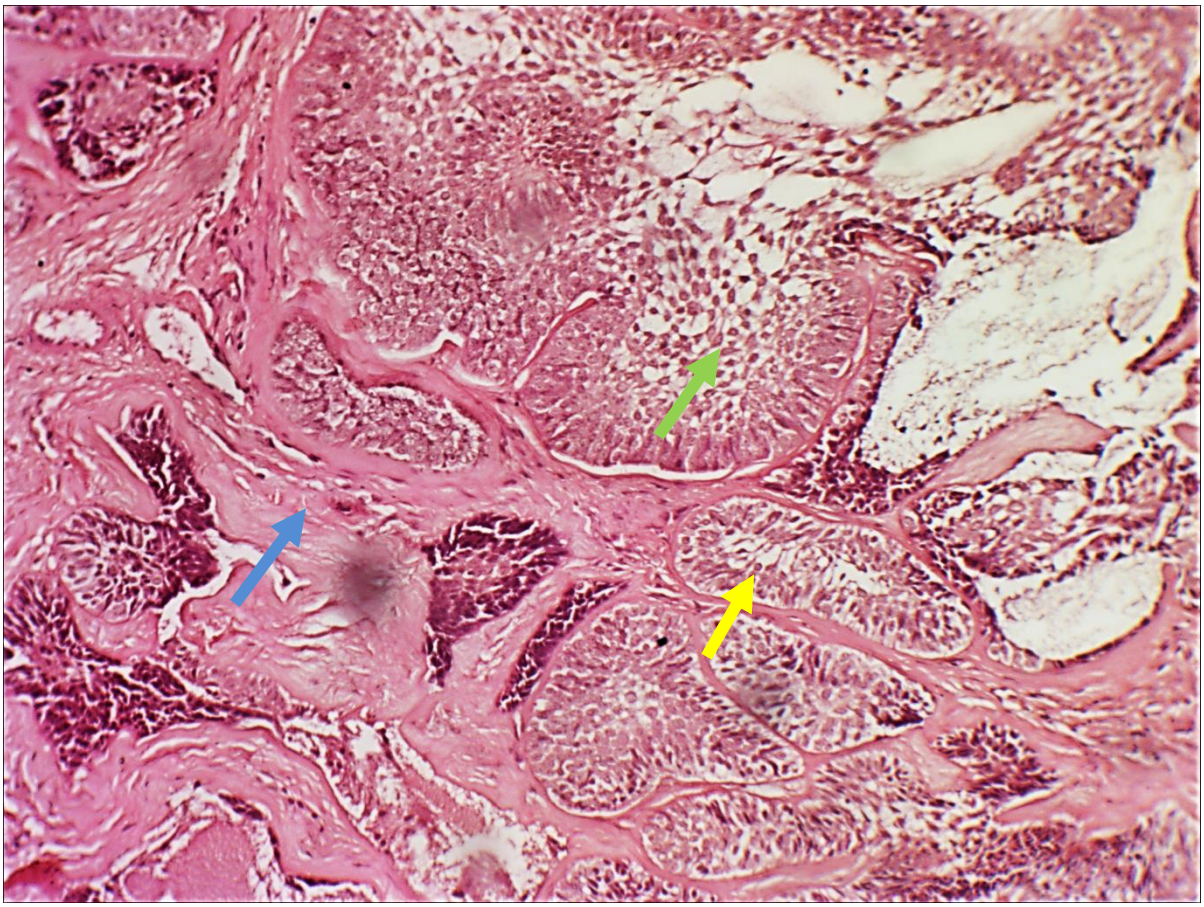

Figure (12) Photomicrograph of a histopathological section of desmoplastic ameloblastoma showing islands and follicles within a collagenous stroma (blue arrow). Some of the follicle reveal a peripheral palisading columnar cells (yellow arrow) surrounding satellite reticulum like cells (green arrow), other show proliferating basal cells, cellular and nuclear pleomorphic of the follicular cells. This histopathological picture is consistent with aggressive ameloblastoma (Hematoxylin and Eosin ×100).

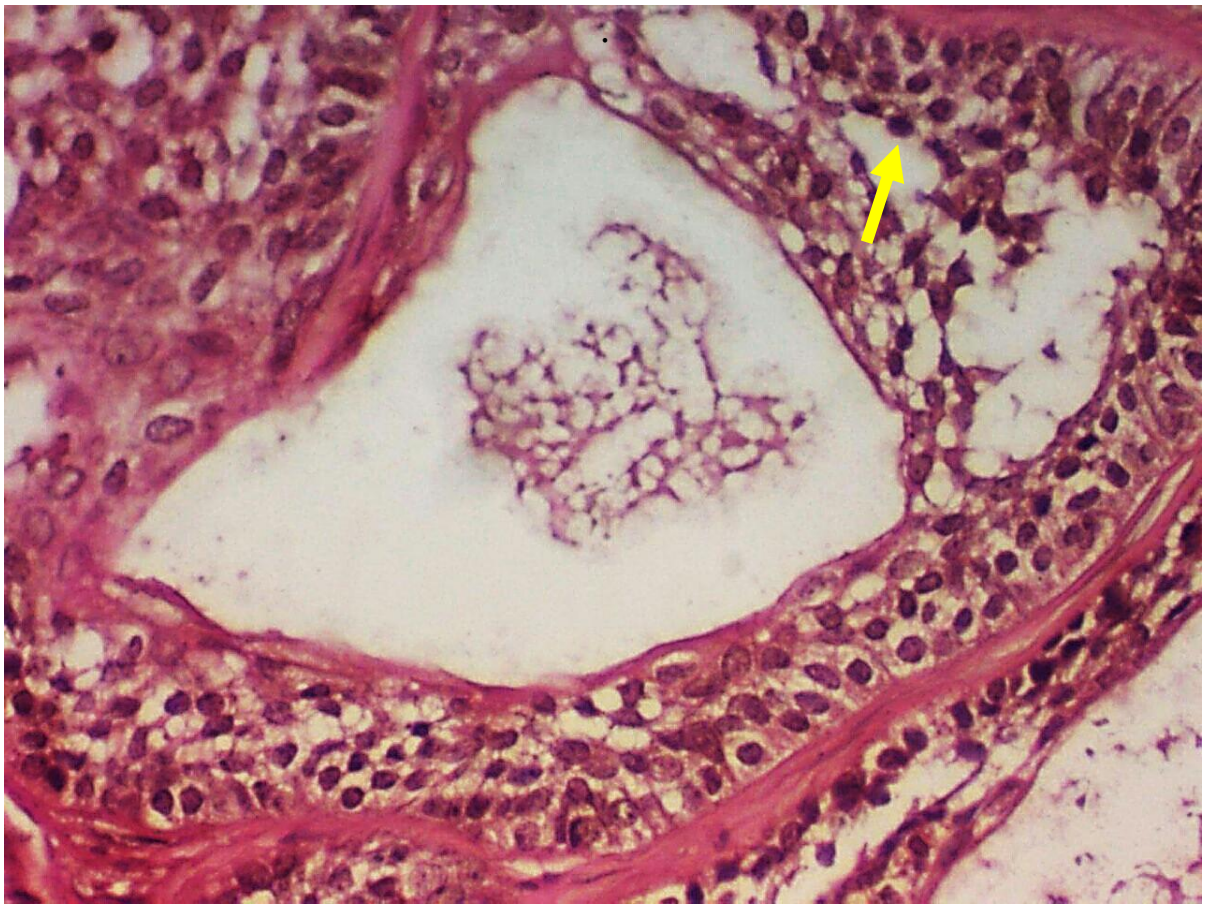

Figure (13) Photomicrograph of a histopathological malignant plexiform ameloblastoma .yellow arrow malignant ameloblastic cells (Hematoxylin and Eosin ×400)

The Immune Reaction of the EGFR in the Ameloblastomas.

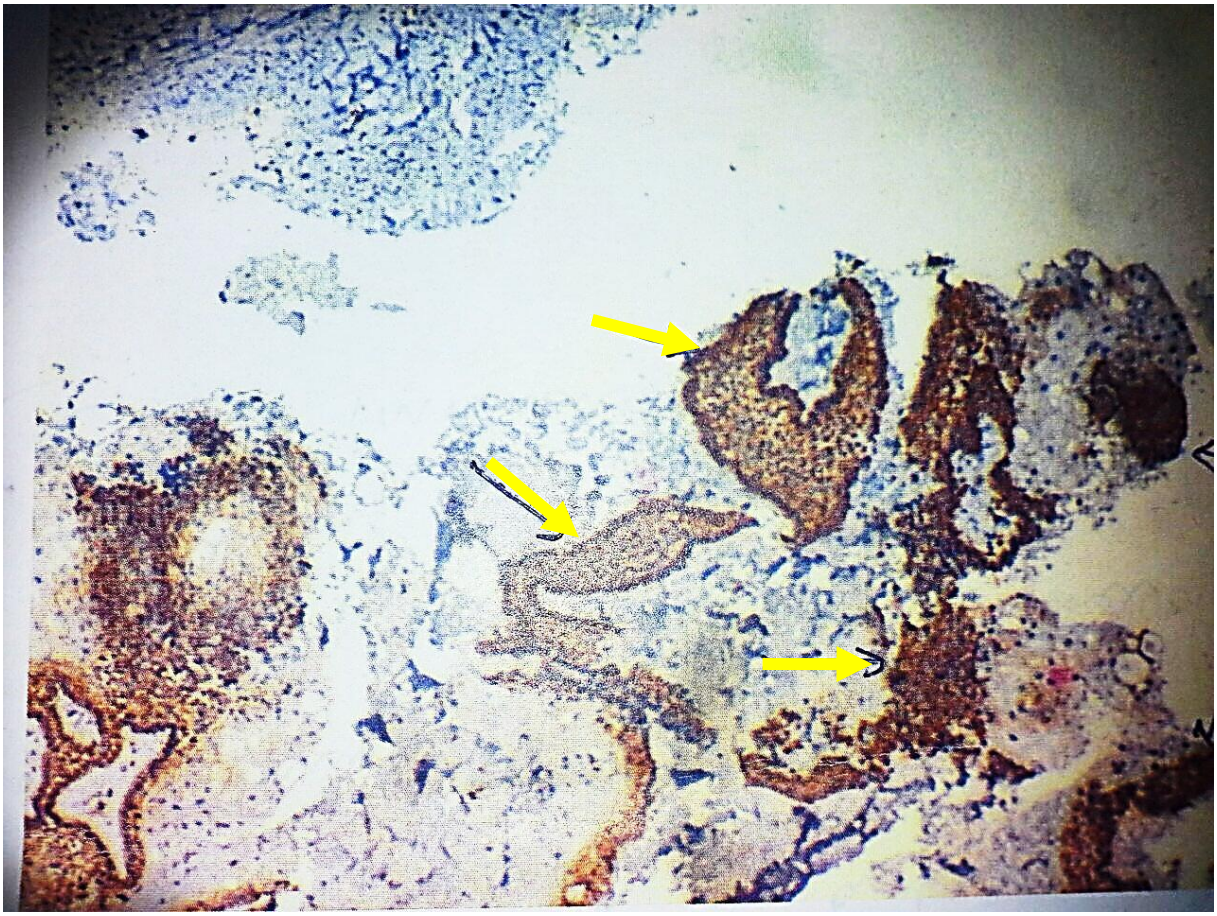

Figure (14): Photomicrograph of a histochemical section yellow arrow reveal the ameloblastoma showing moderate basal staining for EGFR in the groups of ameloblastic cells. (EGFR immuno- stain × 100).

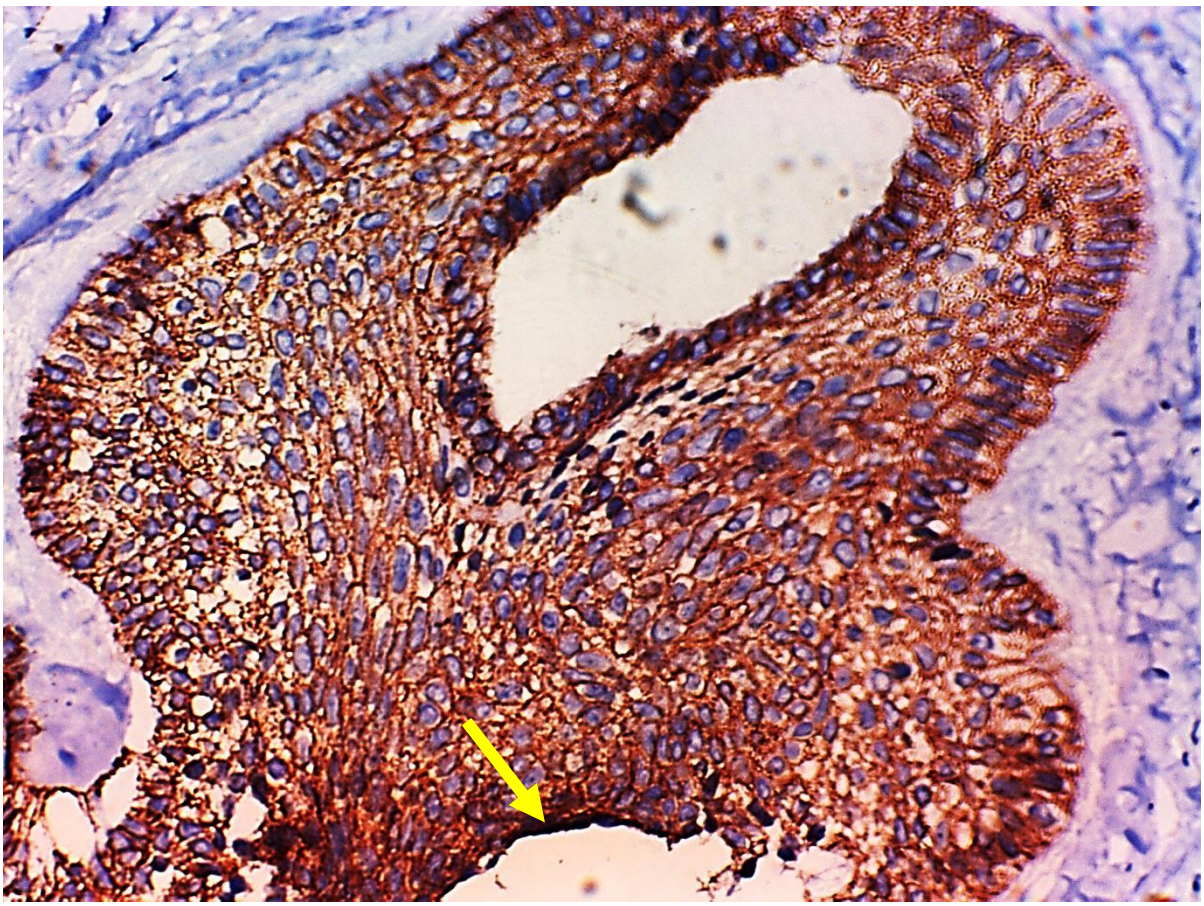

Figure (15): Higher power view of the previous case showing marked positive membranous staining of ameloblastic cells yellow arrow (EGFR immuno stain, x 400)

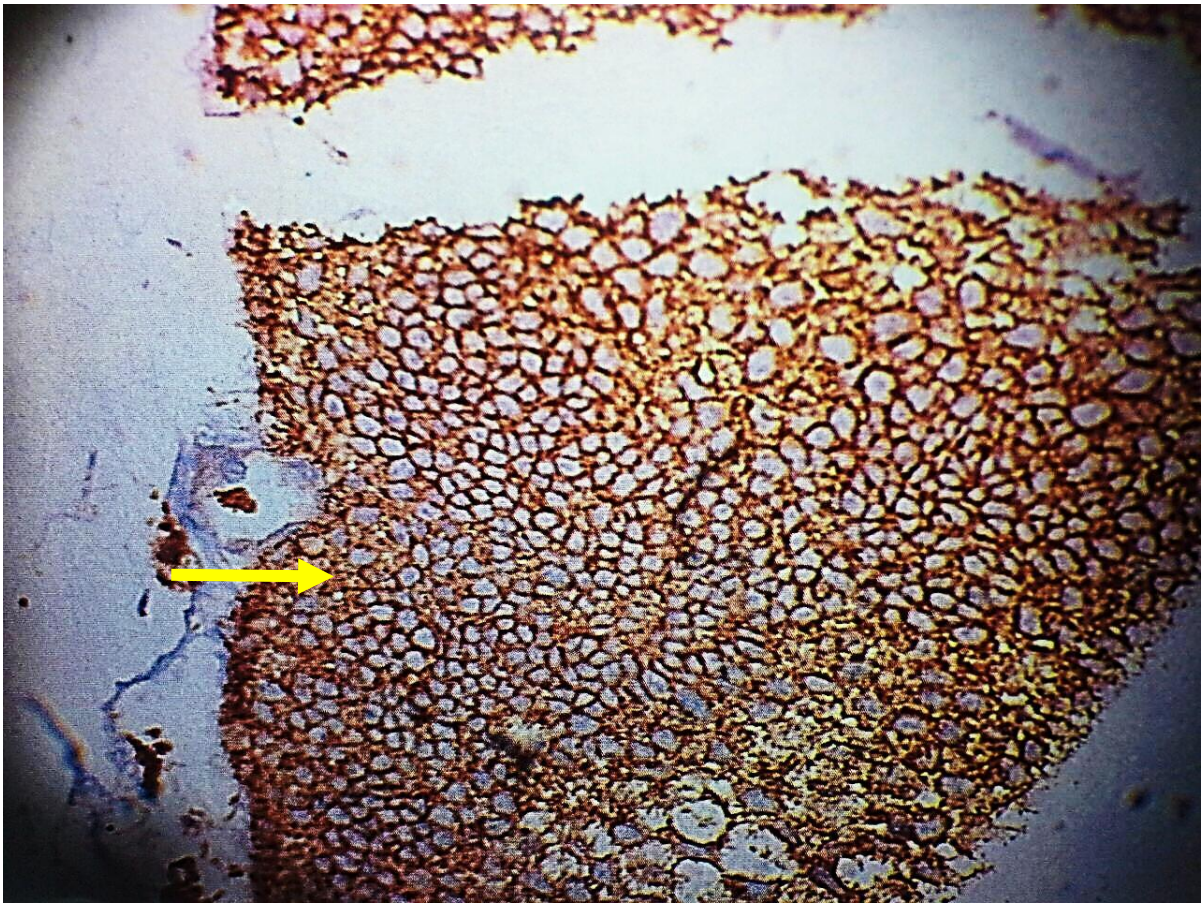

Figure (16): Photomicrograph of a case of follicular ameloblastoma showing marked positive staining of the ameloblastic cells.Yellow arrow (basal stain with EGFR x100)

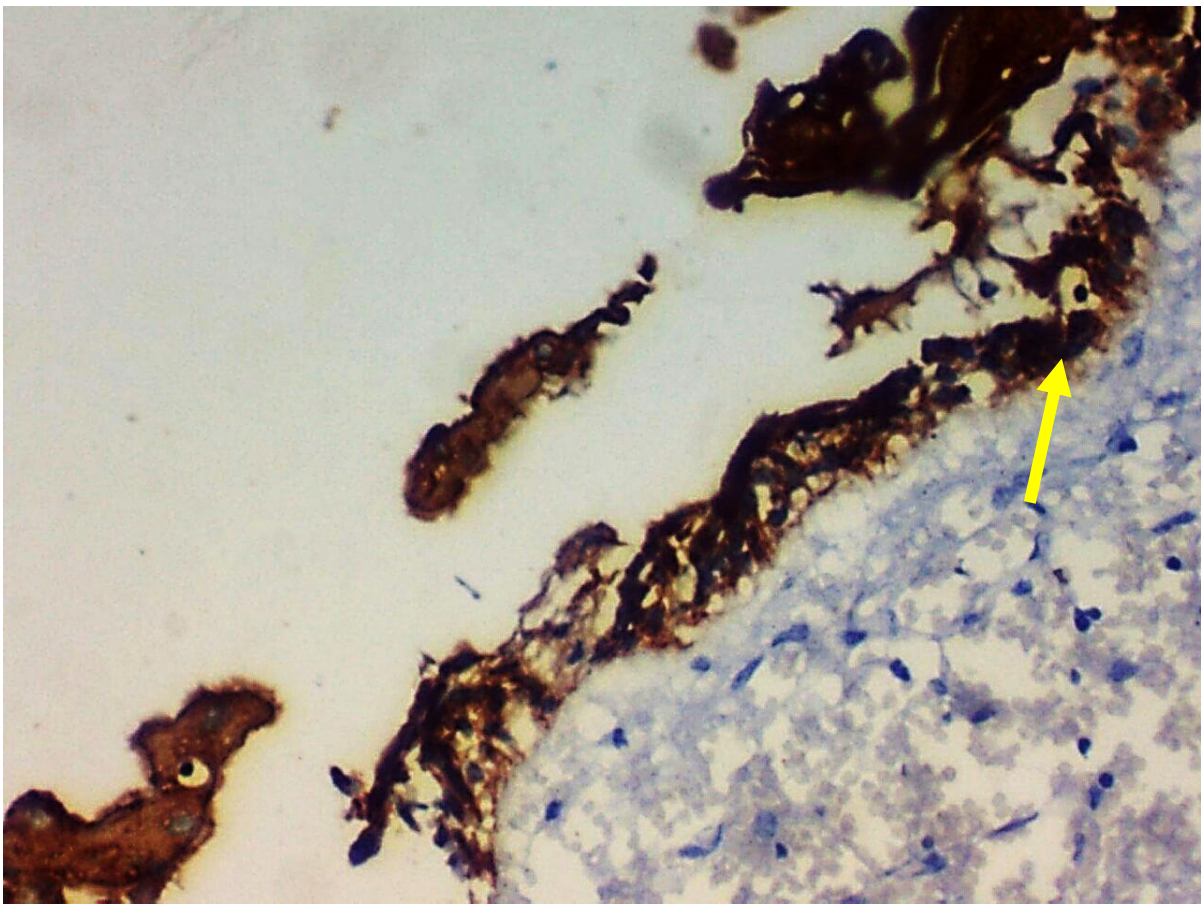

Figure (17) Photomicrograph of histochemical section of cystic ameloblastoma showing strong brownish membranous, focal and basal staining of ameloblastoma cells with EGFR green arow. (EGFR immuno stain ×400).

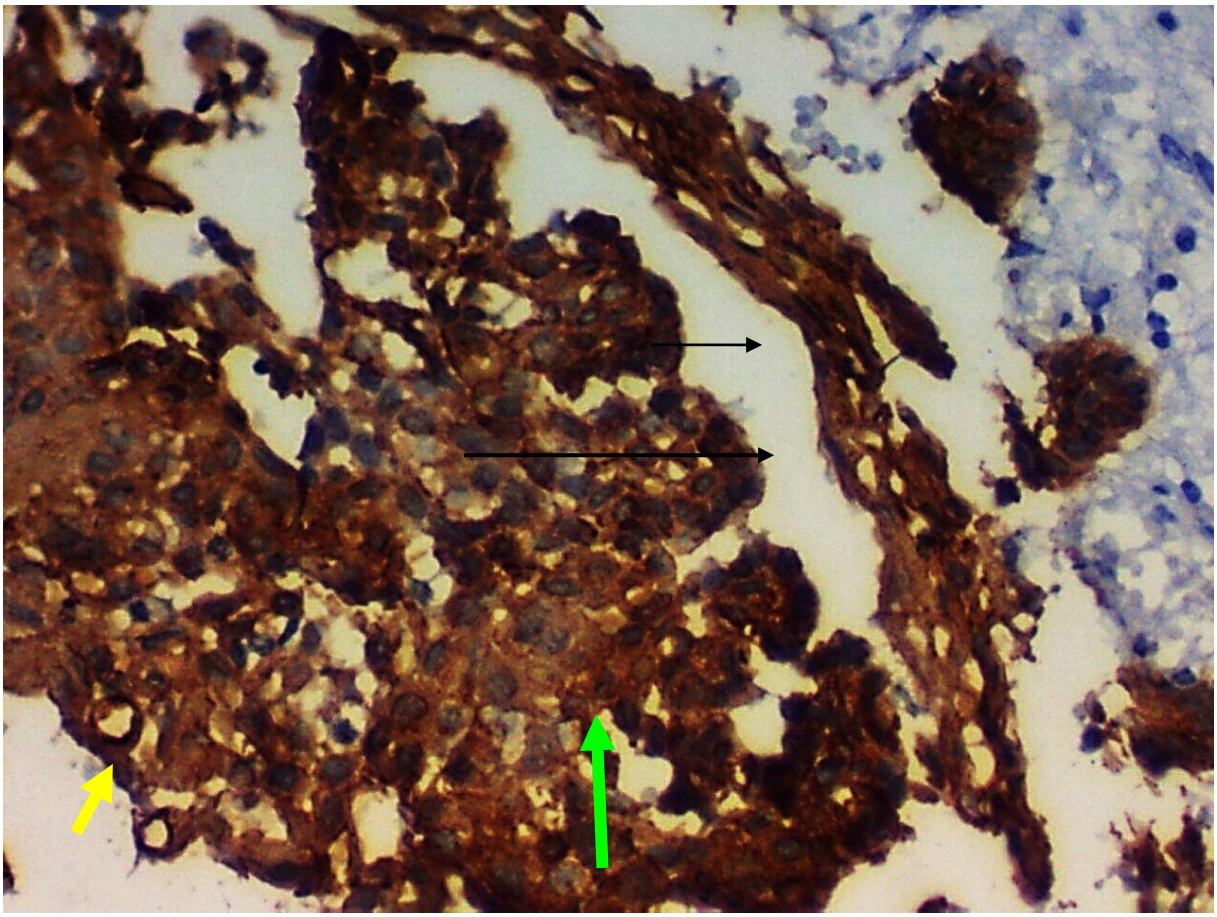

Figure (18): Photomicrograph of a histochemical section of the desmoplastic ameloblastoma showing strong diffuse positive staining. The brownish stain combines membranous (yellow arrow) and cytoplasm (green arrow) (EGFR immuno stain × 400).

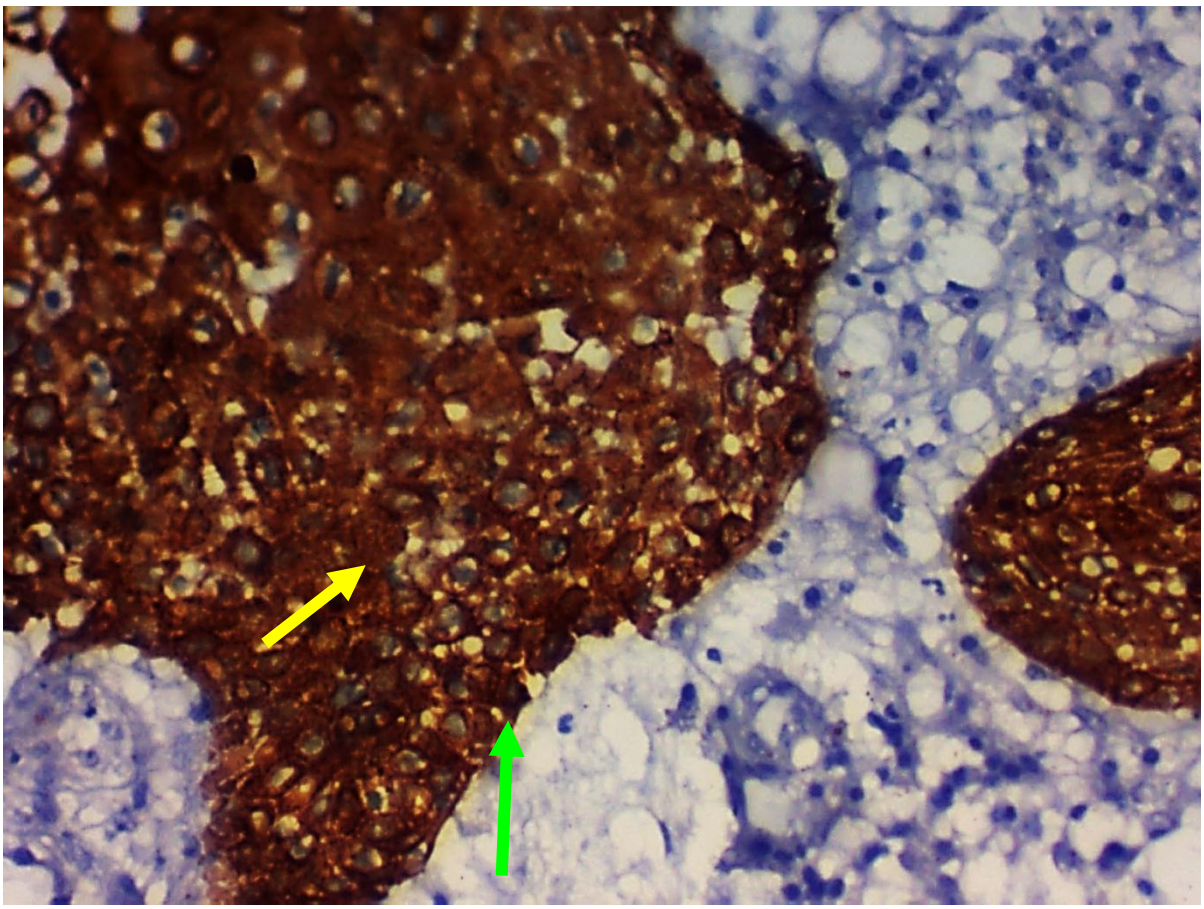

Figure (19): Photomicrograph of a case of the follicular ameloblastoma showing strong posietive staining of the ameloblastic cells basal (green arrow) and supra basal (yellow arrow) stain, combine membranous and cytoplasm (EGFR immuno stain ×400).

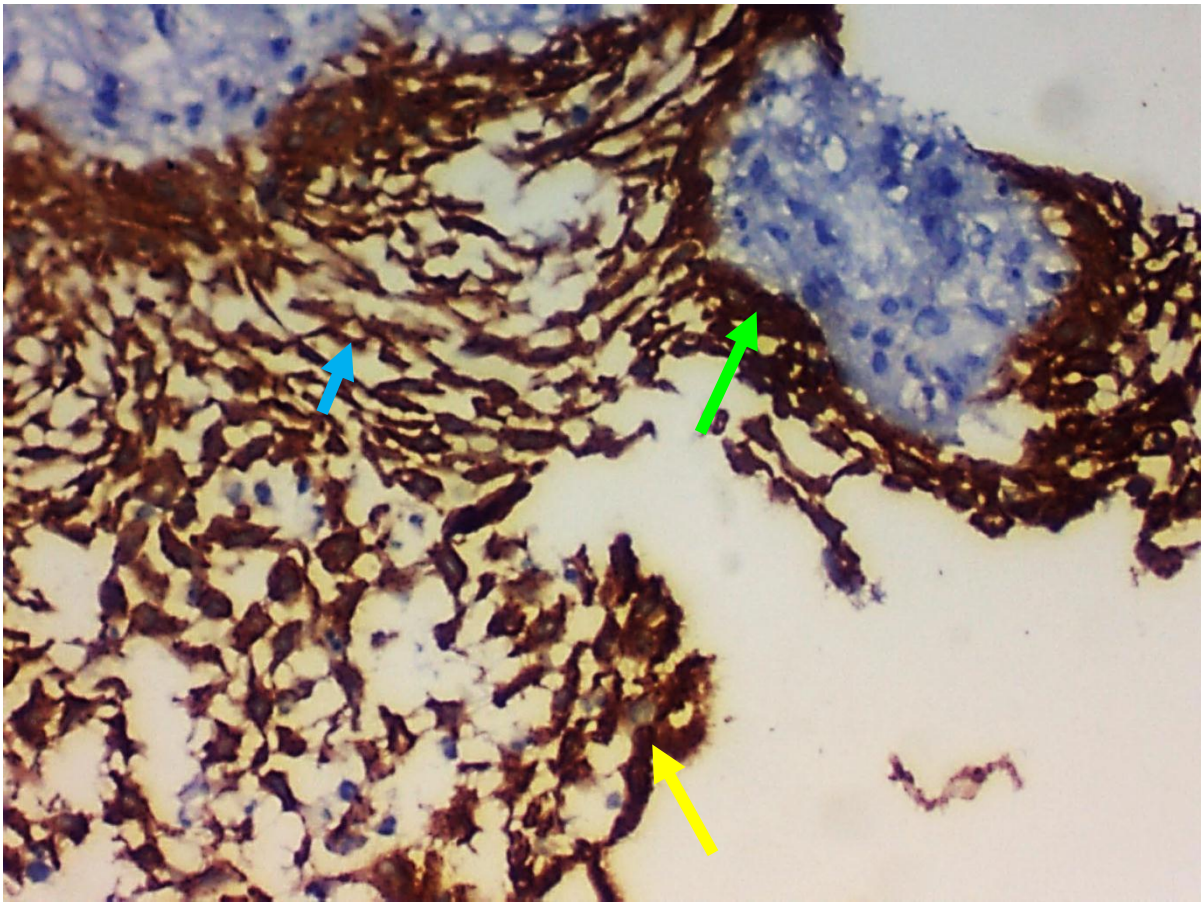

Figure (20): Photomicrograph of a histochemical section of the follicular ameloblastoma showing moderate diffuse positive staining. The stain shows at basal and supra basal, combine membranous (blue arrow). Cytoplasmic (green arrow) and nuclear (yellow arrow) (EGFR immuno stain ×400).

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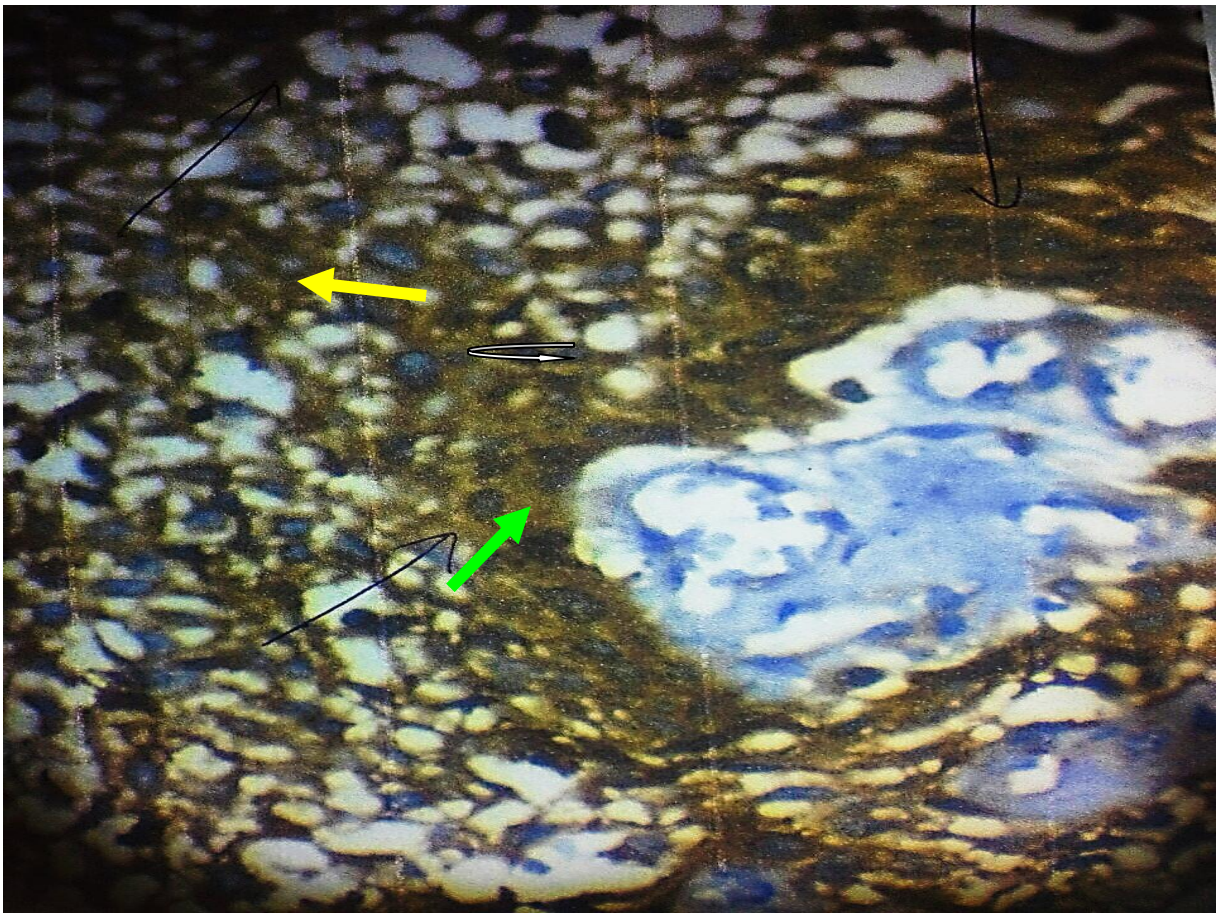

Figure (21): Photomicrograph of a histochemical section of ameloblastoma showing strong brownish staining of the **malignant** cells (EGFR immuno stain ×400), diffuse, basal (green arrow) and supra basal (yellow arrow) (staining with EGFR.

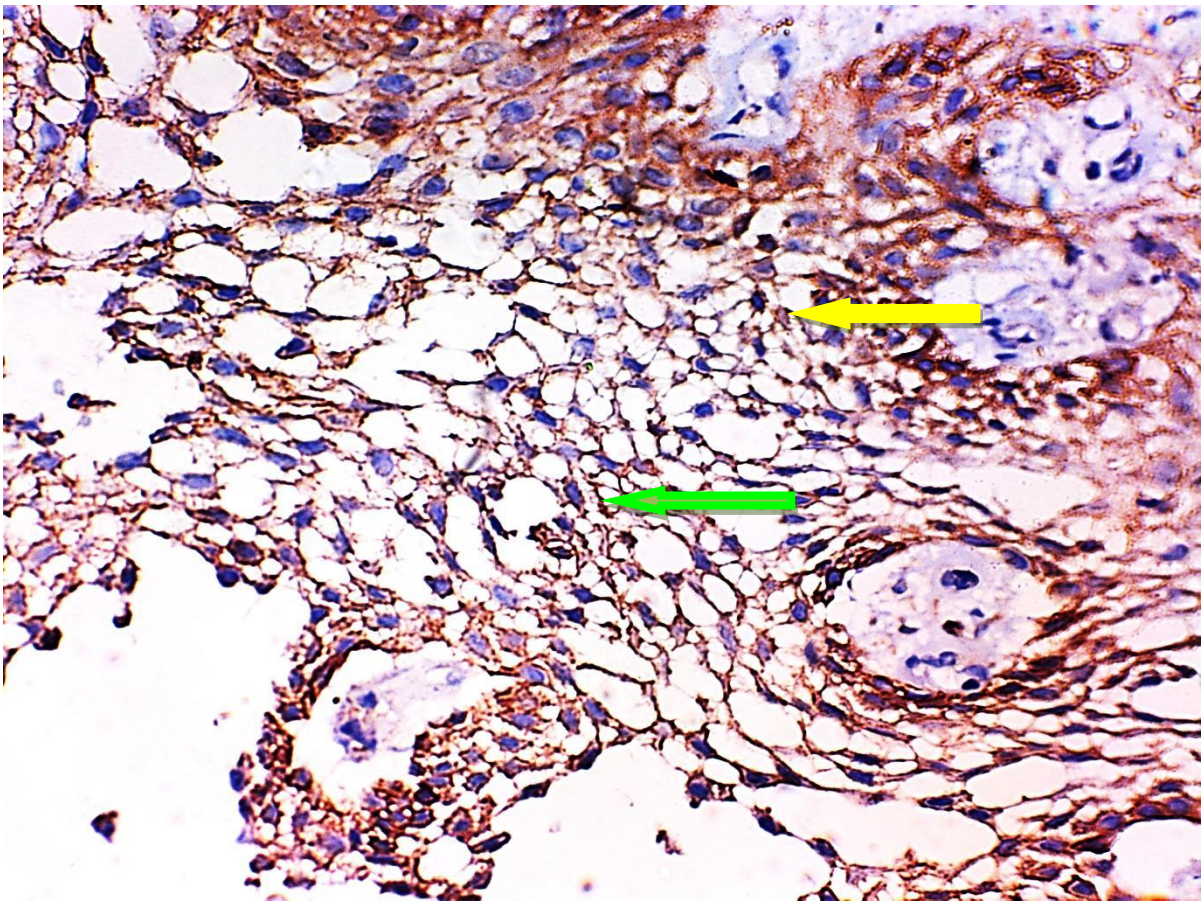

Figure (22): Photomicrograph of a histochemical section of ameloblastoma moderate membranous, basal (yellow arrow) and supra basal (green arrow) staining of satellite reticulum like cells (EGFR immuno stain ×400).

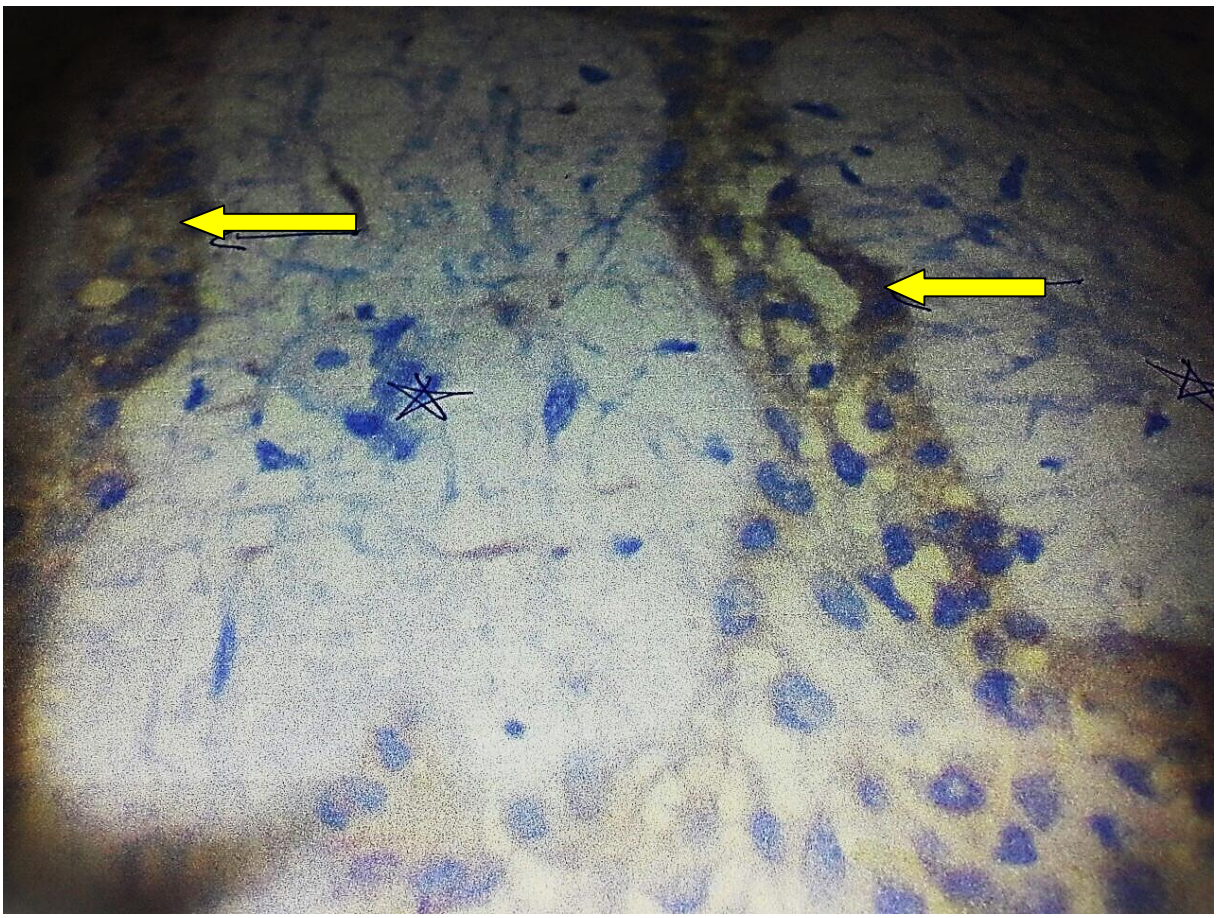

Figure (23): Photomicrograph of a histochemical section of plexiform ameloblastoma weak stain showing cords of ameloblastoma cells separated by connective tissue stroma (EGFR immuno stain ×400), brownish focal staining yellow arrow.

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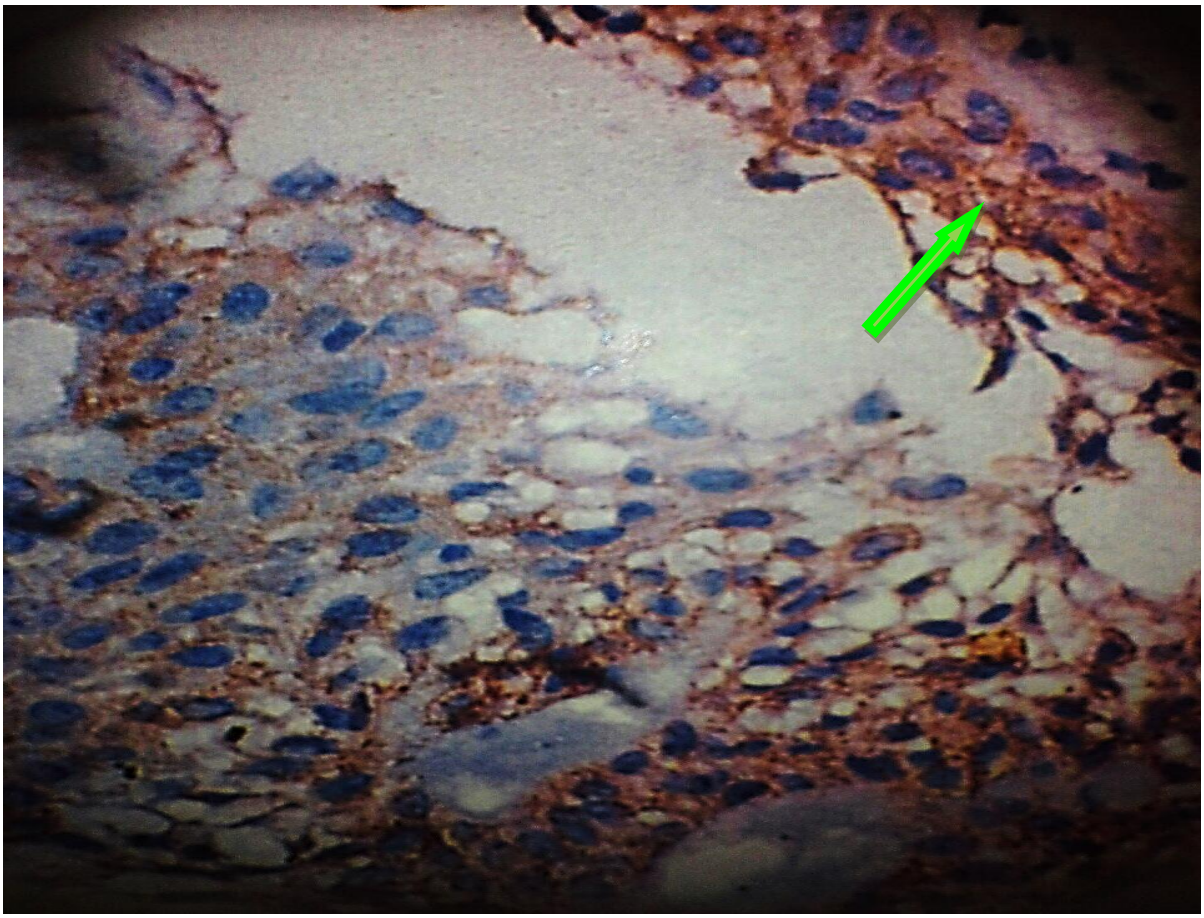

Figure (24): Photomicrograph of a histochemical section of ameloblastoma shows mild membranous basal staining of ameloblastic cells green arrow (EGFR immuno stain ×400).

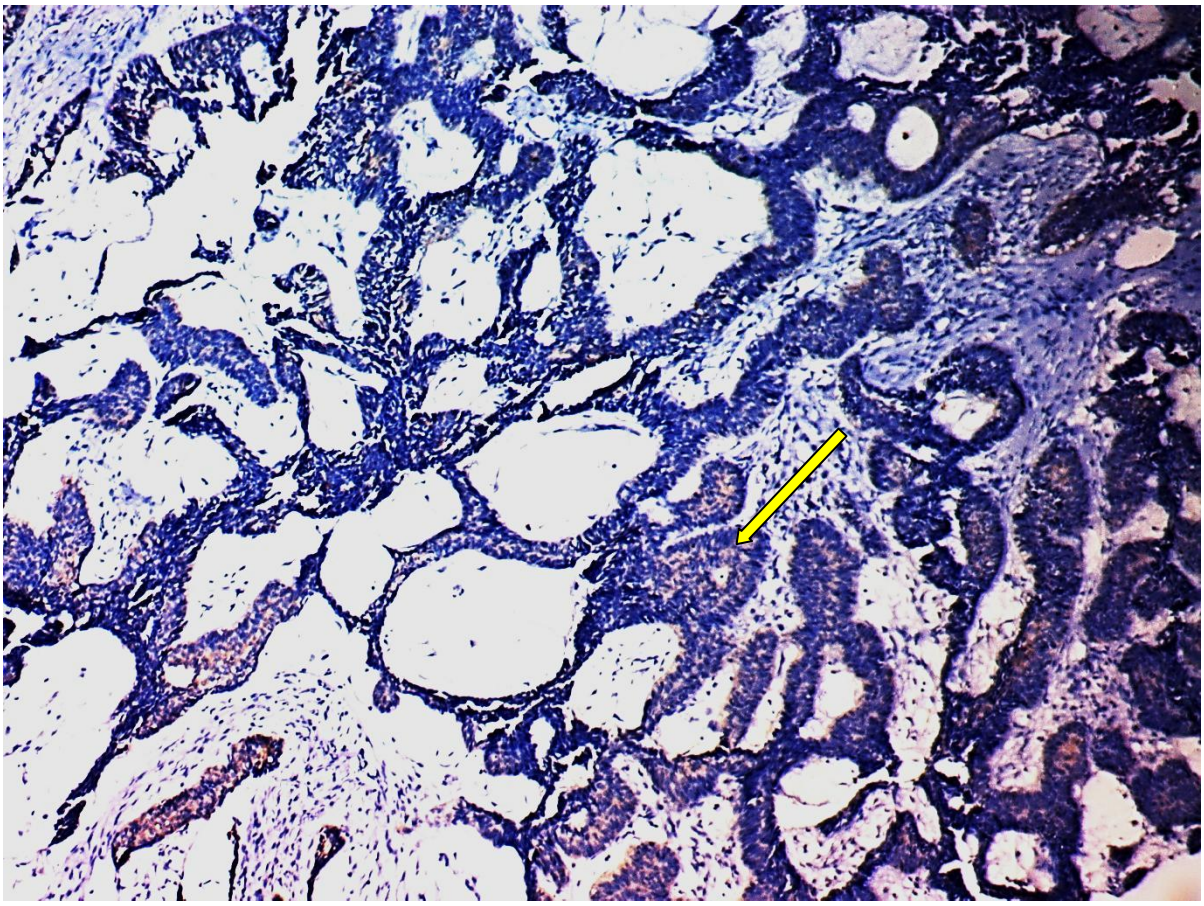

Figure (25): Photomicrograph of a case of ameloblastoma showing negative staining of the ameloblastomic cells for EGFR cells yellow arrow. (EGFR immuno stain $\times$100).

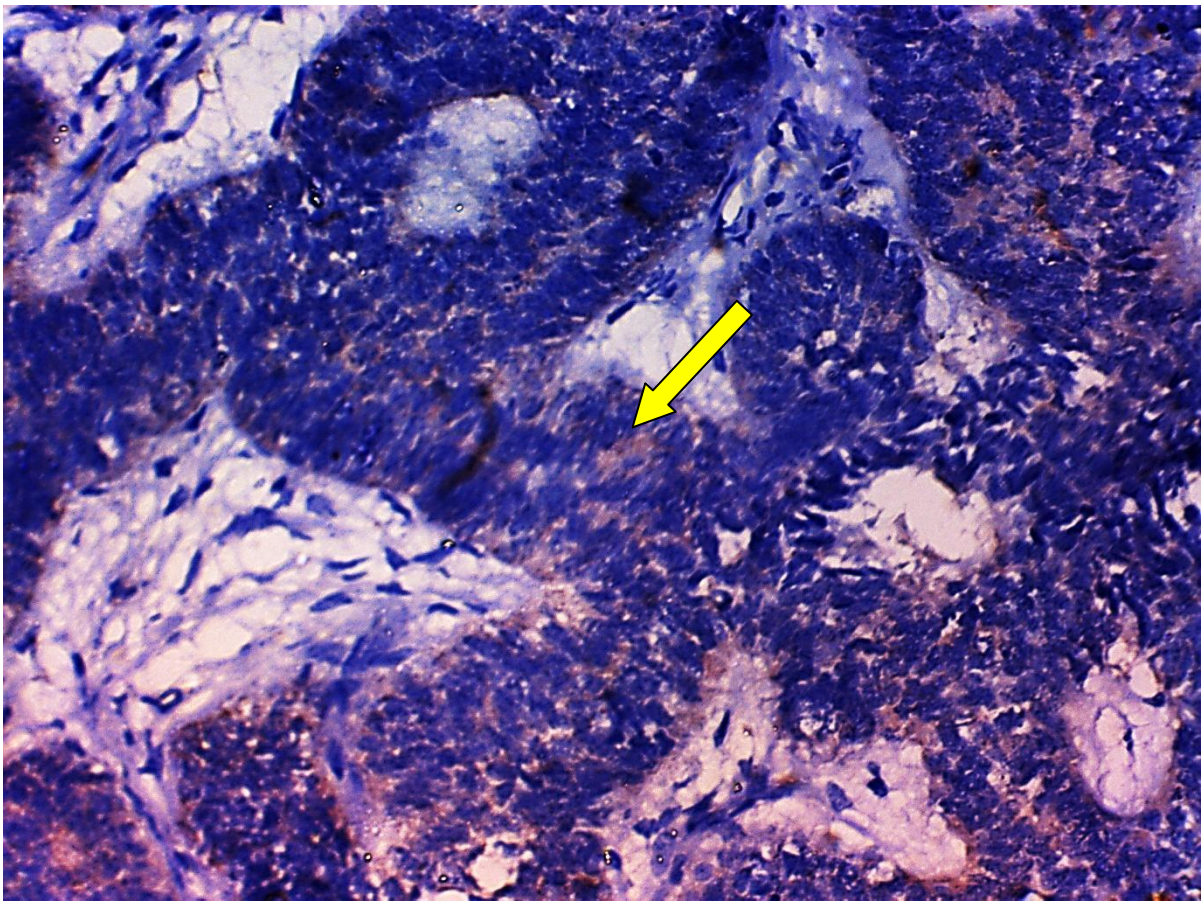

Figure (26): High power view of the previous case showing negative staining of the ameloblastic cells yellow arrow (EGFR immuno stain x 400).

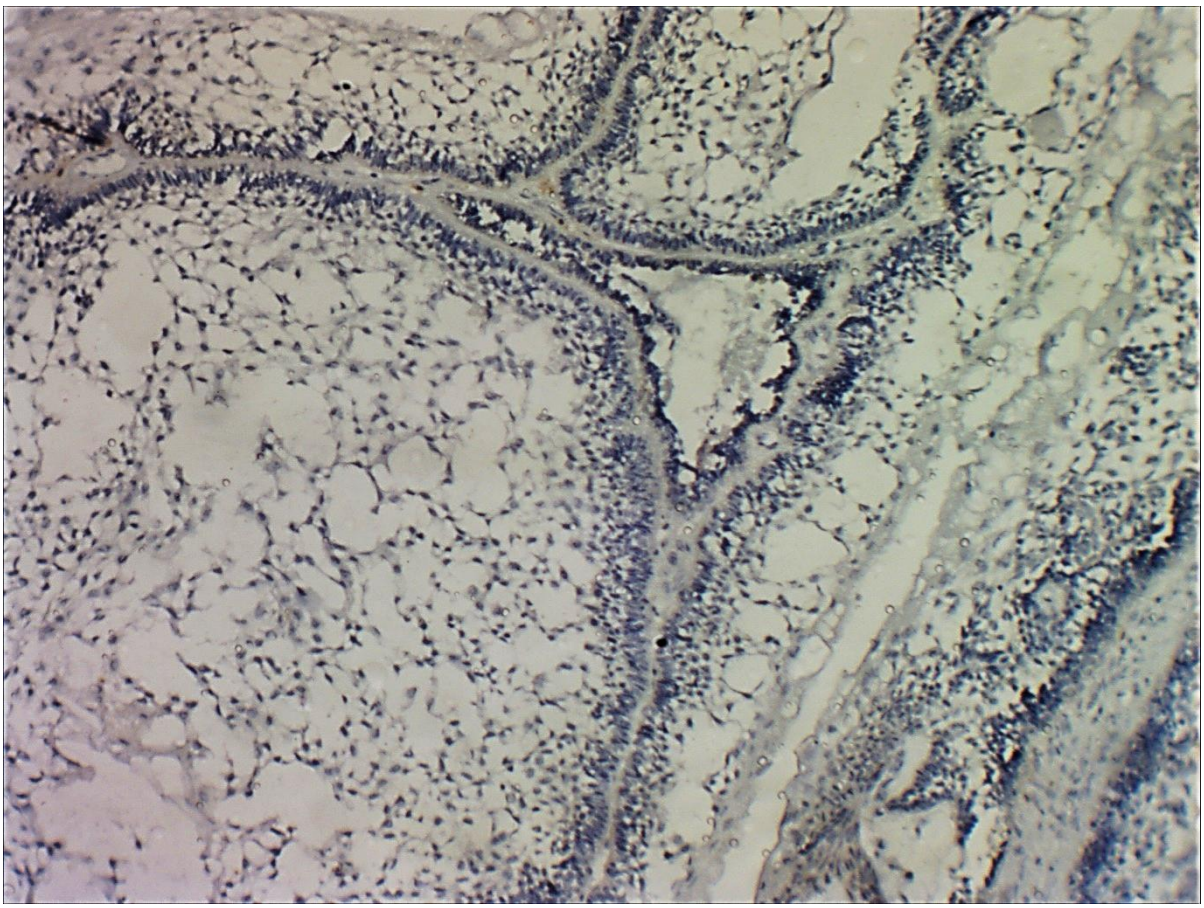

Figure (27): Photomicrograph of a histochemical section of follicular ameloblastoma showing negative staining of ameloblastoma cells by (EGFR immuno stain ×100).

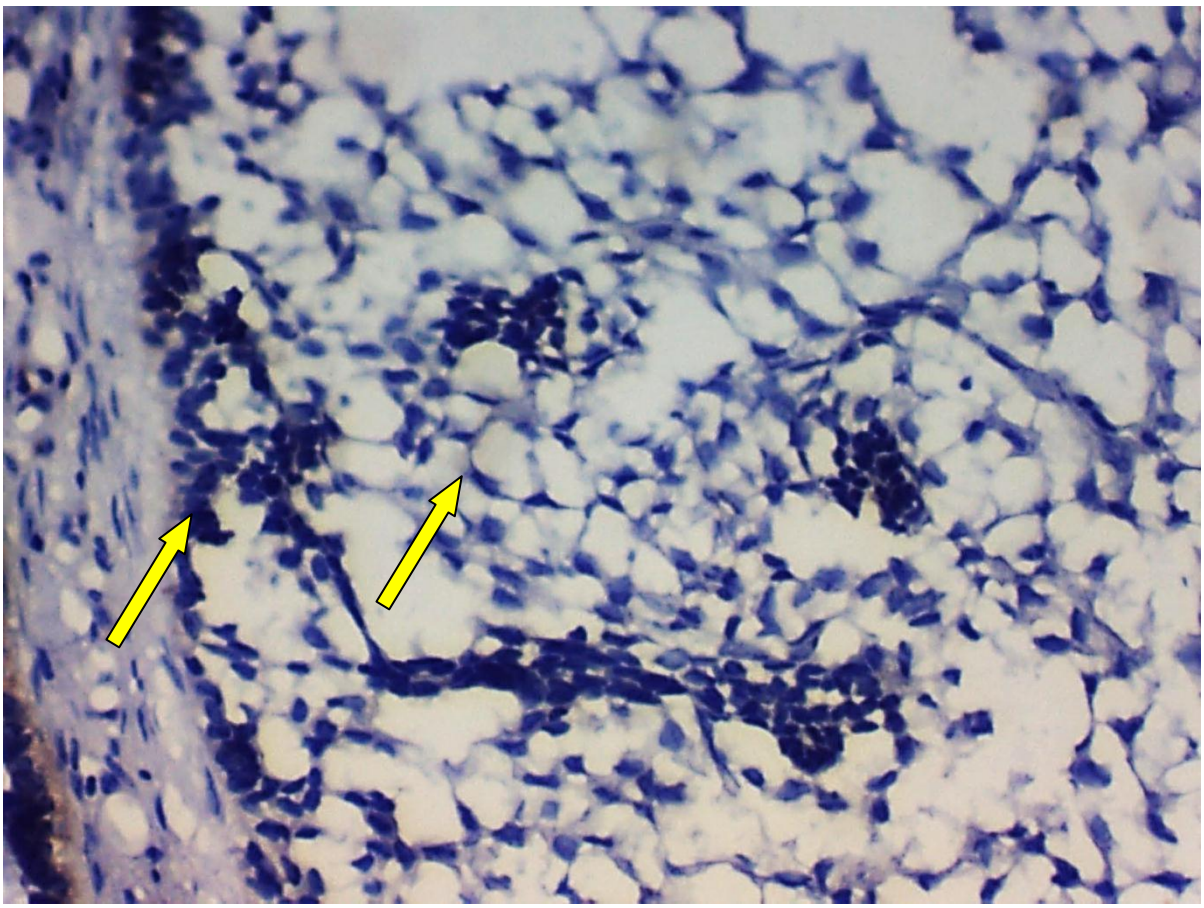

Figure (28): High power of previous case of follicular ameloblastoma showing negative staining of ameloblastic cells yellow arrow (EGFR immuno stain ×400).

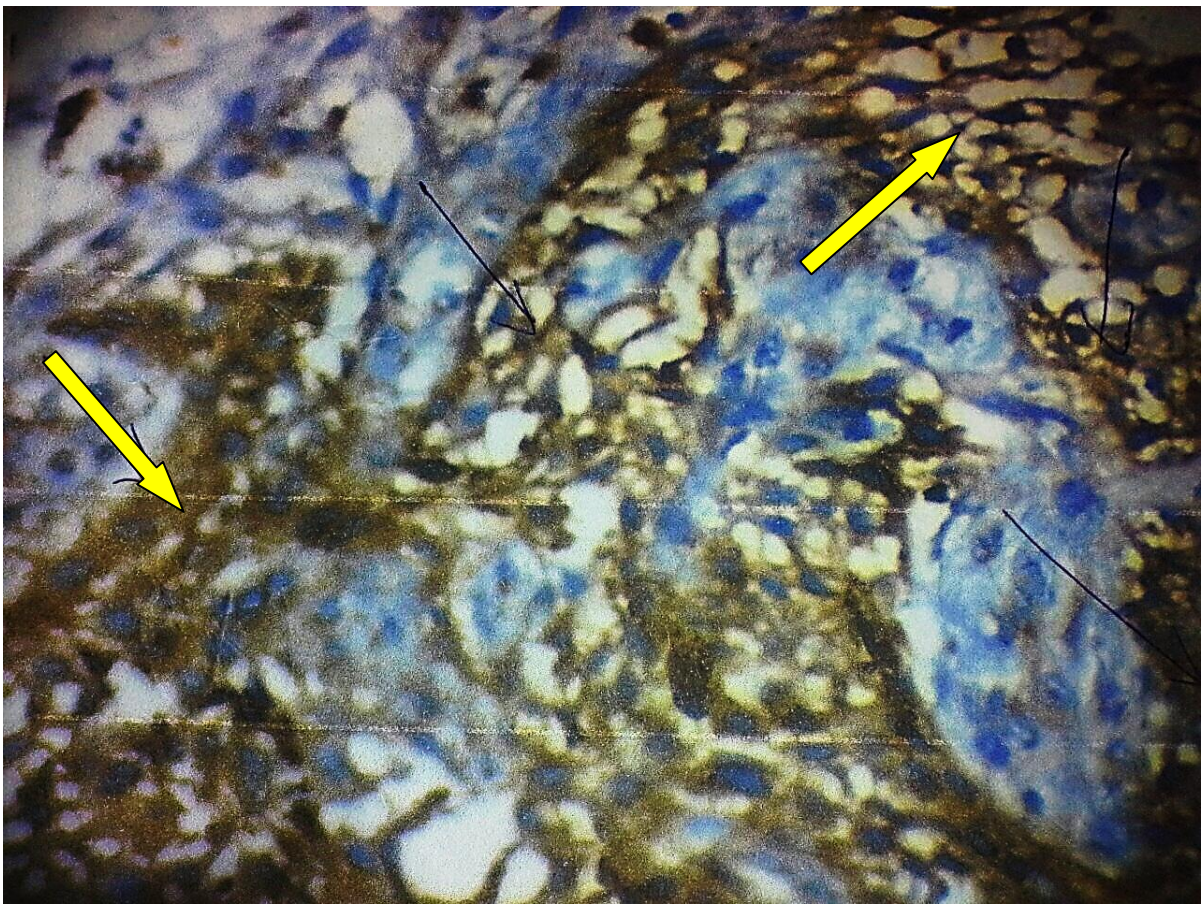

Figure (29): Photomicrograph of a histochemical section of case of ameloblastoma showing moderate brownish staining of the tumor cells yellow arrow (EGFR immuno stain ×400).

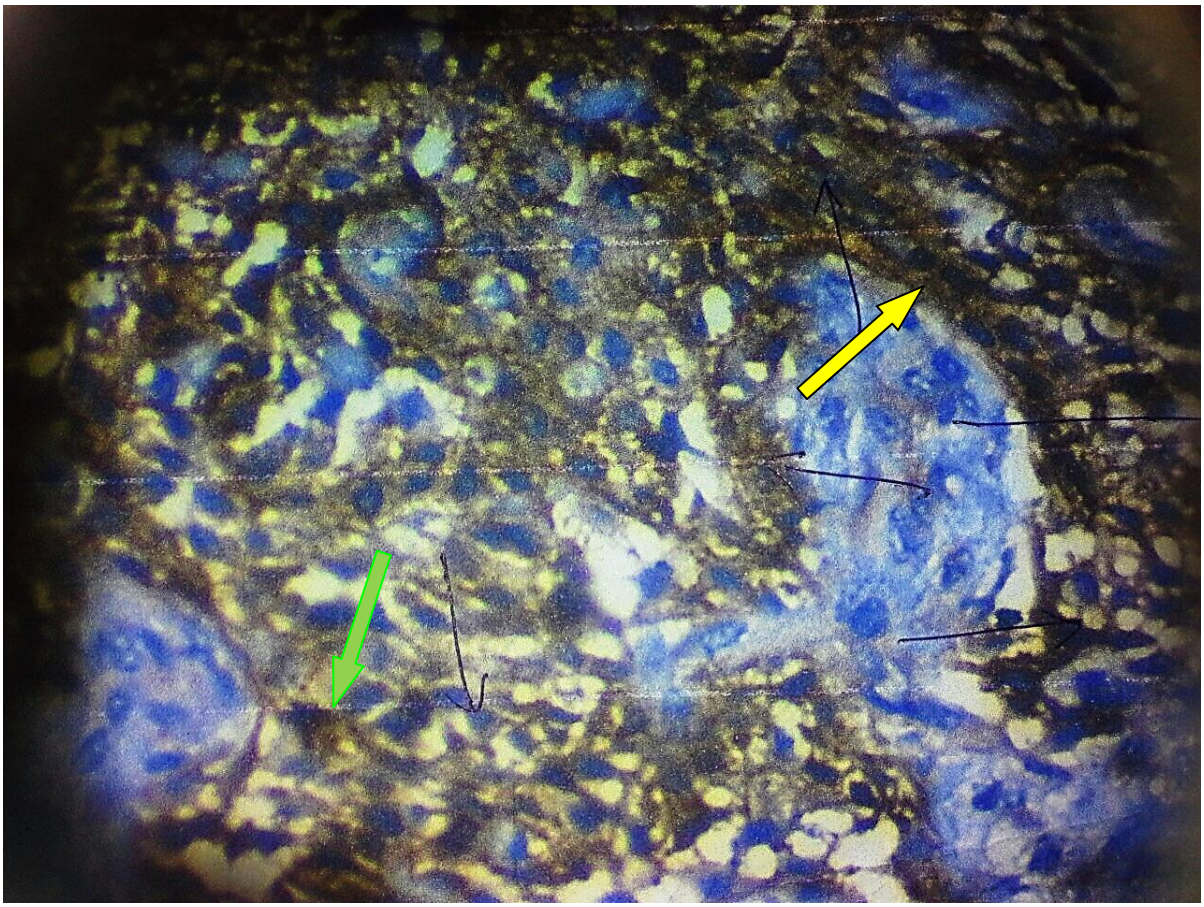

Figure (30): Photomicrograph of a histochemical section of ameloblastoma showing marked staining of malignant cells, basal and supra basal yellow and green arrow (EGFR immuno stain ×400).

Chapter 6
Discussion

Discussion

The present study was conducted in the Faculty of Dentistry, Benghazi University, from January 1995 to 2010 December. In this study twenty-five cases of ameloblastoma, nationality of the cases were Libyan and residency from Benghazi city in both 88% whereas the non-Libyan and residency from out-side Benghazi were account very small number.

In this study we recorded the age of the subjects ranged from15 to 50 years with mean age 29.1 years and SD was 10.586 years with Male: Female ratio was 1.5: 1. The males more slightly than females. Most of the cases were found in the second to fourth decades. Same results with Corio et al, [34] had reported the mean age of occurrence to be 30.1 years with no gender predilection and, Akrish et al. 2007, recorded that the mean age of occurrence to be 25 years and the male to female ratio being 1.5 : 1 [104].

Our finding showed that 52% which represents more than half of cases of Ameloblastoma mainly in right side of the mandible, while 44% in left sides of the mandible and only 4% in both sides. The posterior side of the mandible was the most favored site (21) 84 %, and (2) 8% of the lesions in the anterior region, 8 % are located in the area of the molars or the ascending ramus, 4% in the premolar rejoin. Same results of the posterior mandible was the most site in both the reports [101,102], the age, sex and site in the present cases described here agree with the data given in the literature [95].

Our results consistent with other study , in Nigerian population shows that the mandible (80% of ameloblastomas), 70% are located in the area of the molars or the ascending ramus areas, 20% in the premolar region, and 10% in the anterior region, about 10-15% of ameloblastomas are associated with a non-erupted tooth. Similar study found that the commonest area was mandible [104]. Furthermore, our results similar to a published data, that showed the ameloblastoma is a rare benign odontogenic tumor, representing only 1% of all

tumors and cysts of maxilla and mandible [106]. It involves either sex [107], and can occurs at any age, 50% occurs between age of 20 and 30 years mandible [102, 105]. From literature ameloblastoma is a benign odontogenic neoplasm that has locally invasive behavior. Ameloblastomas can be further divided according to World Health Organization (WHO) classification of odontogenic tumors, into four types: solid or multicystic, extraosseous or peripheral, desmoplastic, and unicystic types according to the clinical and radiographic features. Histologically, six histological variants including the follicular, plexiform, acanthomatous, granular cell, desmoplastic, and basal cell ameloblastomas are found [88,108].

It was also observed in the present study that the histopathological features of twenty-five cases of ameloblastoma the majority of cases were cystic 48 %, plexiform represents about 32 % whereas, follicular were seen of 16% of cases also desmoplastic were account only in 4% of cases. More than half of cases of ameloblastoma approximately 65% were solid multicystic which is more aggressive four of these cases diagnosed as malignant ameloblastoma while, the minority 35 % were unicystic Which is benign **.**

The present study consistent with Turki [91], study which demonstrated that the most common types are plexiform and follicular and the other uncommon variants include acanthomatous, granular cell, desmoplastic and basal cell types. The most prevalent histological subtype is the follicular variant, followed by the plexiform and the acanthomatous variants [9,91].

In this study histological subtype of ameloblastoma such as Granular cell, Acanthomatous and Basal cell were not observed (zero %). It records most of ameloblastoma were focal which represents 48 % and only 40% were diffuse reactions while 12% of ameloblastoma were negative reactions.

Our result was in line with the results of a study in India, which showed that the ameloblastoma is the most common epithelial odontogenic

tumor of the jaw with several histological varint ; follicular, plexiform, acanthomatous, desmoplastic, and granular cell and basal cell types. The basal cell ameloblastoma is a rare histological variant which tends to demonstrate microscopic features similar to cutaneous basal cell carcinoma and basaloid squamous cell carcinoma [(94).]

Rarity of basal cell variant of ameloblastoma in conjunction with atypical histological feature constitutes a puzzling paradox. Hence, long-term follow-up at regular intervals after surgery is recommended [(107),] while in Kiran study reported that more than 80% of all ameloblastomas are solid or multicystic variants, with unicystic ameloblastoma being an important clinicopathologic form of ameloblastoma and occupying the remaining 20% of the cases along with peripheral ameloblastoma [(110).]

Other literatures have been a nearly agreement with our study , such as Sharma and his colleagues, they reported that granular cell ameloblastoma also is a less common histological subtype of ameloblastoma [(111).] The finding are to somewhat similar to those in previous studies reported of Unicystic ameloblastoma tends to affect young adolescent/younger patients. According to a case report of unicystic ameloblastoma (UA) in a 65 -year-old male reported a rare case that was occurred in 7th decade. Unicystic ameloblastoma can only be diagnosed based on histopathological features and cannot be predicted on clinical and radiological grounds alone.

The examination of the entire lesion through sectioning at varying levels is mandatory for securing the final diagnosis. Unicystic ameloblastoma is believed to be less aggressive and should be treated conservatively, furthermore, the study reported that Unicystic ameloblastoma (UA) refers to those cystic lesions showing clinical, radiographic, or gross features of a mandibular cyst, but on histological examination show a typical ameloblastomatous epithelium lining part of the cyst cavity, with or without

luminal and/or mural tumor growth. It accounts for 5-15% of all intraosseous ameloblastomas [36].

Another case report study , done in Nigeria for ameloblastoma of mandible of a 12 year old girl had been reported that ameloblastoma is a benign epithelial odontogenic tumor, is locally aggressive. This tumor comprises about 1% of tumors and cysts arising in the jaws. It appears most commonly in the third to fifth decades and with equal frequency between sexes. Ameloblastoma prevalently occurs in the mandibular molar and the ramus areas[105, 106]. Recurrence frequently appears after inadequate treatment. They are usually benign in growth pattern but frequently invade locally and occasionally metastasize[88]. The histopathological processing of the tumor revealed a plexiform ameloblastoma predominantly composed of epithelium arranged as a tangled network of anastomosing strands.

Clinical examination revealed a large, expansive mass found in the ascending ramus and molar region of the mandible and it was not associated with a non-erupted tooth. The swelling was hard, painless to palpation and covered by normal mucosa. The term "plexiform" refers to the appearance of anastomosing islands of odontogenic epithelium in contrast to a follicular pattern [88].

On the other hand, the histological appearances are characteristic in recent studies in which described the Plexiform ameloblastoma of mandible. They said although ameloblastoma is one of the most common odontogenic tumors, its final diagnosis can only be confirmed with a histopatological examination[113].

In addition, A study in Nigerian population, demonstrates the histologically of ameloblastoma is characterized by the proliferation of epithelial cells arranged in a collagenous fibrous connective tissue stroma of conjunctive vascular tissue in locally invading structures that resemble the enamel organ at different stages of differentiation [105].Radiographically,

ameloblastoma of the mandible can mimic other tumors of the mandible, such as, the odontogenic keratocyst, aneurysmal bone cyst, fibrosarcoma, or a giant cell tumor. A high index of suspicion of ameloblastoma will help triage the patients for further appropriate management [89,114].

While the Literature discussed, a report of unusual case although the clinical presentation was suggestive of a malignancy, the histological features were not sufficient to warrant the lesion as malignant, the features of epithelial dedifferentiation were evident at post-operative histopathological evaluation but no proof was available to authenticate frank metastasis or carcinoma. [39].

Ramphul et al 2018 stated that there is no differences in cell type and pattern between peripheral and central ameloblastoma and the clinicians should encouraged to share their experience on rare histological variant of Ameloblastoma [115].

A study in 2010 by Taoudi Benchekroun and his colleagues reported that an increased EGFR gene copy number is common in and associated with oral squamous cell carcinoma development in patients with an oral premalignant lesion (OPL) expressing high EGFR, particularly oral squamous cell carcinoma developing at the site of a high expression an oral premalignant lesion ; they also suggest that EGFR inhibitors may prevent oral cancer in patients with OPLs having an increased EGFR gene copy number [116].

While Rajeswari and Saraswathi study in 2012 in India to assess the expression of epithelial growth factor receptor (EGFR) in normal oral mucosa and varying grades of oral epithelial dysplasia, reported that EGFR can be considered as an early marker of a cell proliferation and maturation as well as early marker of epithelial dysplasia and onset of cancer in oral dysplasia[119]. However, further studies with a larger sample size and continuous follow up is suggested to determine its role and significance precisely [118, 119].

Recently, Kreppel and his colleague 2018 also that very little is known about molecular risk factors for Ameloblastoma [120].

In the present study we recorded the majority of cases (21) 86.3% of ameloblastoma with Immune reaction to EGFR were positive while only (4) 14% only negative. Immunoreactions for EGFR. ameloblastoma according to immune response, epidermal growth factor receptor expression (EGFR). According to our study, 21 positively stained ameloblastomas the cells were observed mainly for combined cytoplasmic and membranous staining followed by membranous and then combined of nuclear, cytoplasmic and membranous these results likewise, Bhava study (2015), which records that the follicles predominantly showed combined (cytoplasmic and membrane) staining pattern representing increased proliferative potential similar to squamous cell carcinoma and the basal and parabasal layers of oral mucosa. Follicles with cytoplasm only staining could represent quiescent cells which have the potential to proliferate in the presence of growth factors or they could represent cells which, after differentiation, EGFR is internalized and degraded. Membrane-only staining, on the other hand, may represent an active proliferative cell or a well differentiated cell with decreased or increased proliferative potential depending on the stimuli [(6).]

On the other hand, membrane staining may also be found in physiologic situations like mature cells in the spinous layers of oral mucous membrane, tall columnar ameloblastic cells of reduced enamel epithelium, squamous differentiation in odontogenic rests etc may have increased or decreased proliferative potential depending upon availability of ligands. In contrast, Baumgart et al , study on pericoronal follicles associates cytoplasmic EGFR labeling is with slower proliferation due to internalization of the EGF receptor [(121).]

Combined cell and membrane positivity was related to a more physiologic-type response and membrane only response was associated with greater proliferative potential, epithelium and rests with squamous metaplasia showed mostly membrane only staining, which indicates the possibility that for

squamous metaplasia the EGFR is externalized and used. It was also noted that nests showing squamous differentiation showed more membranous patterns in the center, which is also similar to normal oral mucosa [121].

Another immunohistochemical analysis was performed to determine the localization of epidermal growth factor receptor (EGFR) in ameloblastomas. Ameloblastoma samples were classified into follicular, plexiform, and basal cell types. The number of cases in each category was 17, 19 and 3, respectively. Ameloblastomas, disregarding their histological type, consist of two cell forms: peripheral columnar cells and central satellite cells. The frequency of EGFR expression was much higher in the latter than in the former ($P<0.005$).

On analysis with respect to histological types, the frequency of EGFR expression in columnar cells was not significantly different between the follicular and the plexiform types, but was observed more frequently in the satellite cells in the follicular than in the plexiform ameloblastomas ($P<0.05$). This pattern of EGFR expression was not consistent with the PCNA staining pattern, but was similar to that of keratin expression which we have reported previously. The study suggests that EGFR expression in ameloblastomas is closely associated with tumour differentiation, and squamous differentiation in particular, and the intensity of the staining ranging from moderate to strong stain [122].

In 2003 Vered et al studied immunohistochemical stain of specimens of ameloblastomas showed that was with a monoclonal anti-EGFR antibody (clone 31G7). Positive and negative controls determined specificity of the antibody.A staining score based on the staining intensity and the proportion of stained cells was established, ranging between 0 and 2. Since ameloblastomas are EGFR-positive tumors, anti-EGFR agents could be considered to reduce the size of large tumors and to treat unresectable tumors that are in close proximity to vital structures. Also reported that Ameloblastoma is a locally aggressive

tumor with possible lethal potential. Currently extensive surgery is the most acceptable treatment modality [98].

A study by Kahn in 1989 showed three of ten cases of ameloblastoma in persons under the age of 19 to be positive or human papilloma virus (HPV) by immunohistochemical techniques, whereas none of the cases from older persons showed positivity [123]. Further studies have found various subtypes of HPV associated with a minority of ameloblastomas [124-127], the most common being HPV 6, though a large study using laser capture micro dissection showed no evidence of HPV, arguing against an etiologic association [128].

Non-specific irritation from extractions, dental caries, trauma, inflammation, and nutritional deficiencies has all anecdotally been proposed as etiologies [127] . Until recently, little was known about the molecular aberrations driving ameloblastoma, In addition, the tumor suppressor and anti-apoptotic pathways have been implicated in ameloblastoma pathogenesis [2].

In addition, Filipe Jaeger in Brazil in 2015 reported that the salivary EGF levels in patients with oral leukoplakia do not differ from those in healthy individuals despite the importance of EGF and EGFR in neoplasia. Salivary levels of EGF were not associated with tissue EGF either. So, at this moment, it is not possible to recommend the use of salivary EGF as a biomarker of leukoplakia [129]. However, EGFR expression may occur in two stages, the over-expression in normal and well-differentiated epithelia adjacent to tumour and the upregulation from dysplasia to SCC that may be the result of gene amplification [130].

Also , Abdulmajeed AA, Farah CS study in Australia 2013 stated that Well-designed multicenter studies inclusive of large dataset supplemented by long-term follow up data are required before IHC can routinely serve as an alternative to subjective histopathological diagnosis of oral epithelial dysplasia [131].

Chapter 7
Summary and Conclusion

Summary and Conclusion

1. In general our results concluded that most of ameloblastomas appear most commonly in the third to fifth decades, with nearly equal frequency between sexes. As the site of the tumor found in ameloblastoma prevalently occurs in the mandibular molar and the ramus areas and it was not associated with a non-erupted tooth.
2. Histopathological examination of ameloblastomas when stained with haematoxylin and eosin (H and E) stain. Most of cases were cystic 48 %, plexiform represents about 32 % whereas, follicular were seen of 16% of cases, also desmoplastic were account only in 4% of cases and granular cell, Acanthomatous and Basal cell were not observed in the cases **(**zero %). The study also concluded, the histopathology of ameloblastomas appearance, that the majority of ameloblastoma indicate the biological behavior of the tumors as an aggressive because, most of tumors were cystic and multicystic based on their histological classification, rather than benign, frequently locally invaded and no metastasize was recorded.
3. The majority of cases (21) 86.3% of ameloblastoma are positive for Immune reaction to EGFR , the cells were observed mainly combined of cytoplasmic and membranous followed by membranous, while only(4 lesions) nearly 14% were negative immunoreactions. In the study staining intensity of most of the lesions were ranging from moderate to strong.
4. The majority of the cases (15) of ameloblastoma basal stained to epidermal growth factor receptor while (6) cases of ameloblastoma were basal and suprabasal stained with epidermal growth factor receptor.
5. The study recorded 48% of ameloblastoma were focally stained with epidermal growth factor, while 40% with diffuse reaction.

Chapter 8
Recommendations

RECOMMENDATIONS

1. The present study recommended that the cases of ameloblastoma should be studied carefully, correlating their histological pattern with biological behavior to detect changes that predict the aggressive behavior, so a frequent follow up is necessary for the ameloblastoma to clarify malignant behavior of the tumor **,** because the prognosis is good if the lesion is made with adequate surgical intervention.

2. The study recommend for further research is needed such as the investigation for distribution of p53 and MDM2 immunohistochemical studies. With EGFR in ameloblastoma in order to consider using newly developed anti-EGFR therapeutic agents in cases of unresectable tumor. Further research is needed to verify these finding.

3. Improve the medical records by complete the medical files in the laboratory of oral pathology department at Faculty of dentistry to include all data such as onset of symptom and duration of lesions and if there is any associated diseases, the report of radiography and the management and if there was a history of recurrence and all the information should be computerized.

Chapter 9
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Arabic summary

دراسة مستقبلات عامل النمو البشرة في الورم الأرومي الميناءى الحميد والخبيث في الفكين

إعداد

أمنة عثمان علي الفيتوري

إشراف

أ.د عزام أحمد صالح سلطان

المشرف المساعد

أ.د علي محمد المرتض

الملخص

الورم الأرومي الميناءي هو ورم نووي سني نادر من الفك السفلي والفك العلوي ، مع متغيرات نسيجية متعددة ، ومعدلات تكرار عالية إذا عولج بشكل غير صحيح. وهو ورم غازي محليا غالبا ما يرتبط بالاعتلال وتشوهات الوجه ، ويظهر زيادة في عامل مستقبلات عامل نمو البشرة (EGFR) ويلعب موقع صبغة EGFR دورًا حيويًا في تقييم إمكاناتها التكاثرية ، وعدوانيتها البيولوجية وخيارات العلاج. لقد استهدفنا في هذه الدراسة تقييم الخصائص الإكلينيكية – النسيجية لحالات الورم الأرومي الميناءي ودراسة (فحص المناعة المناعية) – التعبير عن المناعة في EGFR في حالات الورم الأرومي الميناءي لتوضيح دورهم في السلوك البيولوجي للورم.

المواد والطرق: تم إجراء دراسة سلسلة حالة وصفية لخمسة وعشرين مريضا تم تشخيصهم بالأورام الأرومية الميناءية خلال الفترة من 1995 إلى 2010. أجريت الدراسة في مختبر أمراض الفم في كلية طب الأسنان ، جامعة بنغازي. تم جمع البيانات ومراجعتها من ملفات المرضى.

المناعة الكيميائية : باستخدم مستقبلأت عامل النمو البشرة تم إجراء فحص الأنسجة وكان التعبير المناعي رد فعل إيجابي أو سلبي. البيانات التي تم جمعها تم تحليلها باستخدام البرنامج الإحصائي SPSS.

النتائج : تتراوح عمر الحالات من 15 إلى 50 سنة, نسبة الذكور إلى الإناث 1:1.5 وأكثر من نصف حالات الأورام الأرومية الميتائية في الجانب الأيمن من الفك السفلي ، في حين 44 ٪ في الجانب الأيسر للفك السفلي ، وفقط 4 ٪ في كلا الجانبين .إما الفحص النسجي كانت غالبية الحالات الكيسي 48 ٪ و 32% من الحالات الورم الأرومي الميتائي الضفيري وعلى التوالي ,الورم الأرومي الميتائي الجريبي والورم الأرومي الميتائي الصخري 16 ٪ و 4 ٪ من الحالات .

ولم تلاحظ الخلية الحبيبية والخلايا القاعدية في الأورام الأرومية الميتائية. الحالات (21) 86 ٪ كانت ردود فعل مناعية إيجابيا لمستقبلأت عامل النمو البشرة وقد لوحظت الخلايا بشكل رئيسي في الجمع بين السيتوبلازمي والغشائي تليها غشائي فقط ، في حين أن (4 حالات) تمثل 14 ٪ فقط كانت رد فعل مناعي سلبي.

الاستنتاجات والتوصيات: معظم الأورام الأرومية الميتائية تظهر بشكل شائع في العقد من الثالث إلى الخامس. تشير غالبية الأورام إلى السلوك البيولوجي للأورام على أنه عدواني ، لأن معظم الاورام كانت صلدة ومتعدد الأكياس بناءً على تصنيفها النسيجي ، وليست حميدة ولم يتم تسجيل أي انتشار.

دراسة مستقبلات عامل النمو البشرة في الورم الآرومي المينائي الحميد والخبيث في الفكين

قدمت من قبل

أمنة عثمان علي الفيتوري

تحت إشراف

أ.د عزام أحمد صالح سلطان

أ.د علي محمد المرتضي

قدمت هذه الرسالة استكمالا لمتطلبات الحصول على درجة الماجستير في طب وامراض الفم والأسنان

جامعة بنغازي

كلية طب وجراحة الفم والأسنان

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