UNICYSTIC AMELOBLASTOMA: A CRITICAL APPRAISAL

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DECLARATION

I, Suvir Singh, declare that "UNICYSTIC AMELOBLASTOMA: A CRITICAL APPRAISAL" is my own work and that all the sources I have used or quoted have been indicated and acknowledged by means of complete references.

Signed.....

S. Singh

DEDICATION

This thesis is dedicated to: my mom who gave me a goal; my dad who showed me how to attain that goal; and my wife, Nirvana, who helped me realise it.

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ABSTRACT

Robinson and Martinez first introduced the entity of unicystic ameloblastoma in 1977. Since then numerous case reports and series have been published. The evidence suggests that a more conservative approach can be used successfully to treat the unicystic ameloblastoma. The term unicystic is derived from the macro– and microscopic appearance of the lesion, whereas the term unilocular is used in radiological interpretation to describe a radiolucency having one loculus or compartment. Much confusion stems from the fact that a unicystic ameloblastoma might appear not only as a unilocular lesion, but also as what is often interpreted as a multilocular bone defect.

This study was carried out to appraise critically the lesions diagnosed as unicystic ameloblastomas in the Department of Oral Pathology at the University of the Western Cape.

This is a record based retrospective study analysing the unicystic ameloblastomas in the archives of the Department of Oral Pathology of the University of the Western Cape, since the inception of the biopsy service in 1977 to 1999. The sample was analysed according to thereferring hospital, age, sex, race of the patient, site of occurrence, clinical features, and radiological and histological features. The unicystic ameloblastoma can also give an apparently multilocular appearance and the Group 3 histological pattern (Ackermann *et al*, 1988) is the most common.

OPSOMMING

Robinson en Martinez het reeds in 1977 die entiteit unisistiese ameloblastoom bekendgestel. Sedertdien is verskeie gevalstudies en reekse gepubliseer. Van die inligting wil dit voorkom dat 'n meer konserwatiewe benadering gebruik kan word om die unisistiese ameloblastoom suksesvol te behandel. Die term unisisties word afgelei van die makro– en mikroskopiese voorkoms van die letsel terwyl die term unilokulêr gebruik word om in radiodeurskynende letsel met een lokulus te beskryf. Daar is baie verwarring omtrent die feit dat 'n unisistiese ameloblastoom nie net as 'n unilokulêre been defek geïnterpreteer kan word.

Hierdie studie was uitgedra om krities te kyk na letsels wat as unisistiese ameloblastome in die Departement Mondpatologie by die Universiteit Weskaap gediagnoseer is.

Hierdie is 'n rekord gebaseerde retrospektiewe studie wat die unisistiese ameloblastome in die argief van die Departement Mondpatologie van die Universitiet Weskaap sedert die begin van die biopsie diens in 1977 tot 1999, analiseer. Die proefsteek was ontleed volgens die verwysings hospitaal, die ouderdom, geslag en ras van die pasiënt, die plek waar die letsel voorkom, die kliniese tekens en die radiologiese en histologiese kenmerke. Die unisistiese ameloblastoom kan ook 'n waarskynlik multilokulêre voorkoms gee en die Groep 3 histologiese patroon (Ackermann *et al*, 1988) kom die mees algemeen voor.

INTRODUCTION

In the second edition of the World Health Organization's *Histological Typing of Odontogenic Tumours*, an ameloblastoma is defined as 'a benign but locally invasive polymorphic neoplasm consisting of proliferating odontogenic epithelium, which usually has a follicular or plexiform pattern lying in a fibrous stroma' (Kramer, Pindborg and Shear, 1992).

In a survey by Reichart, Philipsen and Sonner (1995) of 1500 publications in the English, German, French, Italian, Portuguese, Korean and Japanese literature, 3677 cases of ameloblastoma were documented between the years 1960 to 1993. This figure indicates the interest in the tumour but not the true incidence, which is defined as the number of new cases of a disease in a defined population over a fixed period of time. Shear and Rachanis (1979) found the age standardised incidence rate of ameloblastoma in the Witwatersrand, South Africa, to have been 5.17 per million population per year over the ten year period 1965–1974.

Currently three distinct types of ameloblastoma, based mainly on clinical behaviour and prognosis, can be distinguished:

i) the 'conventional or classical intraosseous', solid or multicystic ameloblastoma;
ii) the unicystic ameloblastoma; and
iii) the peripheral ameloblastoma (Philipsen and Reichart, 1998).

Robinson and Martinez (1977) were the first to introduce the entity unicystic ameloblastoma. Since then numerous case reports and series have been published. The available evidence suggests that a more conservative approach than that generally employed for the treatment of the 'conventional' ameloblastoma can be used successfully to treat the unicystic

ameloblastoma (Gardner and Pecak, 1980). However, in the case of Group 3 lesions *vide infra* in which there has been mural invasion, a more cautious approach to treatment is advisable (Ackermann, Altini and Shear, 1988).

The definition of the unicystic ameloblastoma has lacked precision. Roos, Raubenheimer and Van Heerden (1994) suggested that the unicystic ameloblastoma might be defined as a unilocular, cystic epithelial odontogenic tumour. Gardner (1999) emphasized that the definition of a unicystic ameloblastoma should be based on two main features: 'the lesion must be unilocular clinically and radiologically; and it must appear on microscopic examination as a single cystic lesion with the epithelial lining consisting of ameloblastoma'.

It is important that in the interpretation of these lesions, two definitions must be strictly adhered to. Firstly, that the term unicystic is derived from the macro– and microscopic appearance of the lesion, whereas, secondly, the term unilocular is used in radiological interpretation to describe a radiolucency having one loculus or compartment. Much confusion stems from the fact that a unicystic ameloblastoma may appear not only as a unilocular lesion but also as what is often erroneously interpreted as a multilocular bone defect. Furthermore, as I shall point out in the discussion, some lesions which appear radiologically to be unilocular, may turn out to be multicystic, and this factor might complicate the accuracy of diagnosis.

My interest in the subject was stimulated by this confusion between the radiological descriptions of unilocularity, multilocularity, and trabeculations; and the term unicystic, which can usually be determined only at operation or in the gross postoperative specimen. The diagnostic difficulty is aggravated for the pathologist when the lesion is not removed

intact. A yet further difficulty for the pathologist is the need to attempt a definitive diagnosis on a small biopsy.

In this study I have tried to clarify these issues in a sample of lesions diagnosed as unicystic ameloblastoma for which radiographs and microscopic sections have been available, including numbers of cases that I have treated myself.

LITERATURE REVIEW

Robinson and Martinez proposed the prognostically distinct entity 'unicystic ameloblastoma' in 1977. Since then, based on its histology, variants have been termed mural, intracystic, cystic or plexiform unicystic ameloblastoma (Ackermann *et al*, 1988). In the literature survey of Reichart *et al* (1995), unicystic ameloblastomas accounted for 6 percent of all intraosseous ameloblastomas.

(a) Clinical Presentation

Leider, Eversole and Barkin (1985) reported a clinicopathologic analysis of 33 cases of unicystic ameloblastomas. The lesions were either asymptomatic and discovered on routine radiographic examination or the patients noted an enlargement of the jaw without pain or parasthesia. All their cases occurred in the mandible with 77.4 percent in the molar–ramus region, 12.9 percent in the mandibular symphysis and 9.7 percent in the cuspid premolar region. Olaitan and Adekeye (1997) reported that swelling, ranging in duration from two months to eight years, was the principal finding in all their cases. Expansion of both buccal and lingual plates was noted in 85.7 percent of cases, whereas buccal expansion alone was seen in the remaining 14.3 percent. Only two of 21 patients complained of pain. In the latter study all the lesions were located in the mandible.

(b) ***Location***

Gardner, Morton and Worsham (1987); and Van Wyk, Thompson and Wyma (1986) each reported a unicystic ameloblastoma in the maxilla. In 1993 Thompson, Ferreira and Van Wyk reported a recurrence of their maxillary case. The lesion had been removed conservatively. Philipsen and Reichart (1998) stated that the location within the jaw bones greatly favoured the mandible with the ratio of mandible:maxilla in different studies ranging from 3:1 to 13:1. All the cases of Leider *et al* (1985) occurred in the mandible with 77.4 percent in the molar–ramus region, 12.9 percent in the mandibular symphysis and 9.7 percent in the cuspid premolar region. The lesion occurs most commonly in the mandibular third molar area and may be associated with an impacted tooth (Ackermann *et al*, 1988; Philipsen and Reichart, 1998). The latter authors referred to those unicystic ameloblastomas associated with an impacted tooth as 'dentigerous' variants and others as the 'non–dentigerous' variants.

(c) ***Age***

Age at the time of diagnosis is significantly younger ($p < 0.001$) for the unicystic ameloblastoma as opposed to the solid or multicystic ameloblastoma (Ackermann *et al*, 1988). In their series the mean age of the patients at the time of diagnosis was 23.8 years (SD 14.9), ranging from 6–77 years, with 48 percent occurring in the second decade and 86 percent occurring in the second to fourth decade. Leider *et al* (1985) found a similar age distribution in their series with a mean age of 26.9 years and 42 percent of lesions occurring in the second decade and 73 percent in the second and third decades. The reports by Philipsen and Reichart (1998) and Eversole, Leider and Strub (1984) have shown that the mean age at the time of diagnosis of the unicystic ameloblastoma correlates closely with the presence or absence of an impacted tooth. Almost 20 years separate the mean age of the 'dentigerous' variant from the 'non–dentigerous' variant (16.5 years versus 35.2 years), but neither set of data was analysed statistically.

(d) ***Gender***

The male to female ratio is approximately 1:1.3 (Leider *et al*, 1984; Ackermann *et al*, 1988; and Philipsen and Reichart, 1998).

(e) ***Race***

Shear and Singh (1978) showed that the age–standardized incidence rates of ameloblastoma on the Witwatersrand was much higher in South African blacks than whites with the ratios being 9.1:1 for black males versus white males and 3.7:1 for black females versus white females. However, they did not separate the unicystics from other forms of the lesion. In the series of Ackermann *et al* (1988) the majority of patients, 51 of 57 cases, were black.

Leider *et al* (1985) showed a different racial distribution with 45 percent White, 33 percent Black, 12 percent Hispanic and 10 percent Oriental. This distribution corresponded with that of the general population in the greater San Francisco Bay area.

(f) ***Radiological Features***

The radiological features of the unicystic ameloblastoma have received relatively little attention in the literature. A M*edline* literature search revealed only one article on this particular aspect, namely that of Eversole *et al* (1984) who conducted an extensive study of the radiological features of 31 unicystic ameloblastomas. Based on the two major categories of:

i) location and relationship to contiguous teeth; and

ii) radiographic configuration and pattern,

they identified six radiological patterns of the lesion:

(a) pericoronal, unilocular;

(b) extensive pericoronal, unilocular;

(c) pericoronal, scalloped;

(d) periapical, unilocular;

(e) interradicular; and

(f) multilocular.

Patterns (a) to (c) were associated with an impacted tooth, whereas (d) and (e) were not.

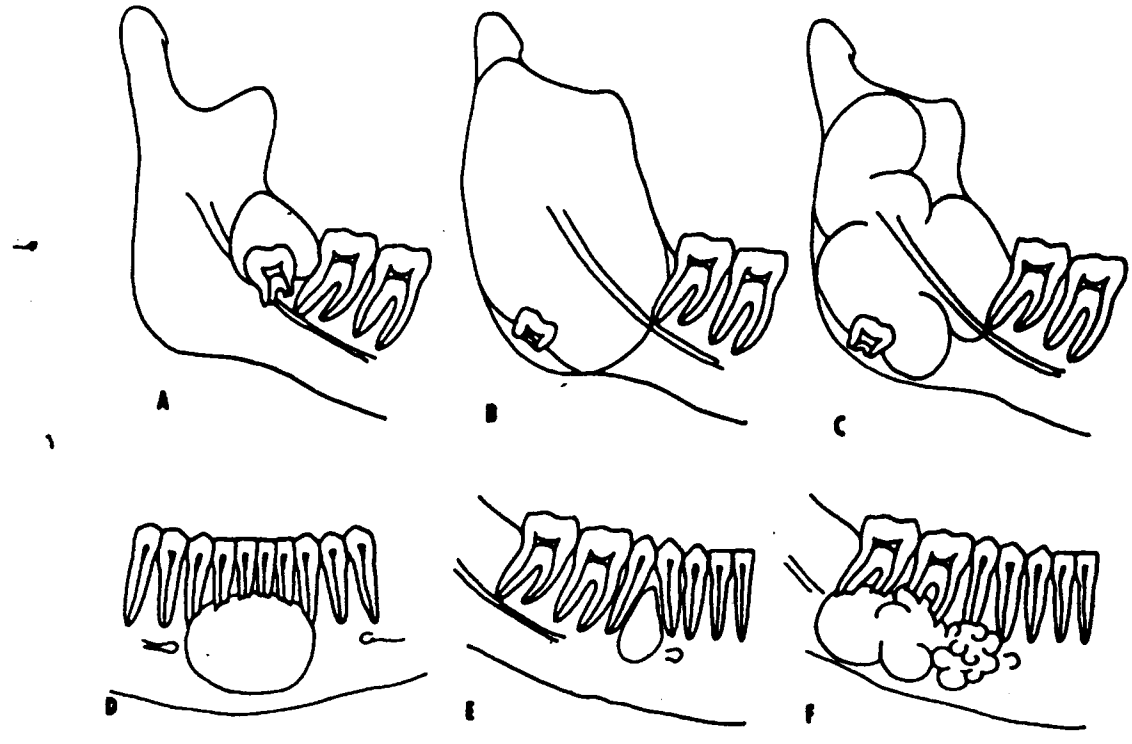

Figure 1: Diagrammatic representation of radiological patterns of the unicystic ameloblastoma. **A**, Pericoronal unilocular. **B**, Extensive pericoronal unilocular. **C**, Pericoronal scalloped. **D**, Periapical unilocular. **E**, Interradicular. **F**, Multilocular. (*Reprinted with permission of* Mosby, Inc. *from* Eversole LR, Leider AS, Strub D. Radiographic characteristics of cystogenic ameloblastoma. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics* 1984; 57:572–577.)

In all six patterns the lesions were radiolucent and well–defined, and occasionally a well demarcated peri–lesional corticated rim could be discerned. Expansion was common. Sixteen of the 31 cases were associated with a mandibular third molar and root development was variably arrested. The lesions not associated with an impacted tooth, showed root resorption or caused root divergence. The unilocular patterns were more common. The ratio of unilocular: 'apparently multilocular' patterns was 13:3 for the 'impaction associated' variant and 8:7 for the others.

When age was considered in relation to radiographic features, it was found that those unicystic ameloblastomas associated with impacted teeth occurred, on average, eight years earlier than those arising independent of impacted teeth. When both impaction and lesional configuration were considered together, it was found that the average age for unilocular impaction–associated tumours was 22 years whereas multilocular lesions without impaction occurred at an average age of 33 years.

Shear (1992) stated that the unicystic ameloblastoma appeared as either a well corticated unilocular radiolucency or the lesion may be trabeculated leading to an erroneous diagnosis of a multilocular cyst. Gardner (1999) raised the point that it is difficult to conceive that a true multilocular lesion may in fact be a unicystic ameloblastoma histologically. He elaborated by stating that a lesion that appears clinically and radiologically to occupy a single cavity, but which has an irregular, scalloped border, is sometimes referred to erroneously as being multilocular, and that such a lesion can be a unicystic ameloblastoma. Conversely an ameloblastoma that presents a radiologic appearance of being unilocular, that is, occupying a single compartment, may be either a unicystic ameloblastoma or a solid or multicystic (classic intraosseous) ameloblastoma. The distinction is made by histopathologic examination. In a personal communication to Gardner, Shear (1999) added that this

distinction might be made grossly at operation and by gross examination of the excised specimen as well as on histopathological examination.

Gardner (1999) stated that the definition of a unicystic ameloblastoma was important. It should be based on two features: the lesion must be unilocular clinically and radiologically; and secondly, it must appear on microscopic examination as a single cystic lesion with an ameloblastomatous epithelial lining.

Furuki *et al* (1997) reported the radiological findings in three recurrent unicystic ameloblastomas that had been initially treated by marsupialization. They identified six stages in the radiographic development of the recurrences:

Stage 1: Bone regeneration in the form of a ground–glass appearance occurred first at the periphery of the marsupialized cavity.

Stage 2: The surface of the regenerated bone soon showed a diffusely sclerotic band.

Stage 3: This became more evident and scalloped.

Stage 4: This scalloping extended downwards or laterally and became rounded.

Stage 5: The radiolucencies then became multilocular with a soap–bubble or honeycomb appearance.

Stage 6: In the final stage the recurrent lesion increased in size.

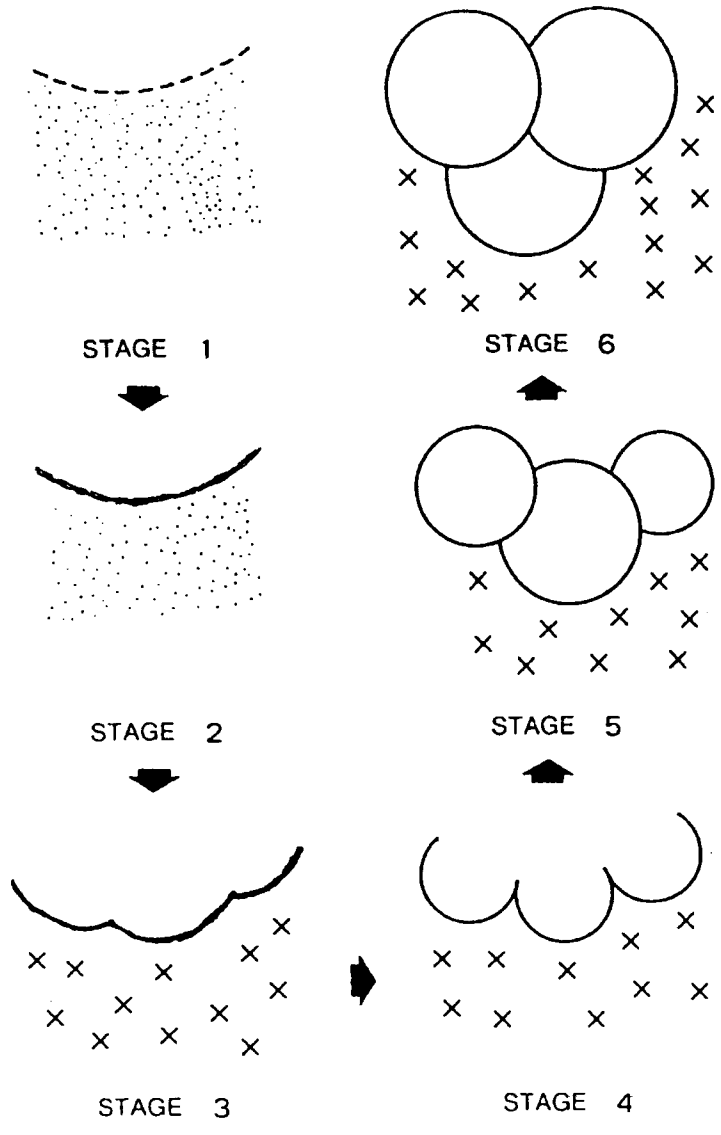

Figure 2: The six radiological stages in the development of a recurrent unicystic ameloblastoma. (*Reprinted with permission of* Nature Publishing Group *from* Furuki Y, Fujita M, Mitsugi M, Tanimoto K, Yoshiga K, Wada T. A radiographic study of recurrent unicystic ameloblastoma following marsupialization. Report of three cases. *Dentomaxillofacial Radiology* 1997; 26:214–218.)

They considered the scalloping of the sclerotic margin as the first obvious radiological sign of the recurrence. All the recurrent lesions showed the soap–bubble or honeycomb appearance radiologically. Furuki *et al* (1997) postulated that this might be the result of multicentric proliferation of the tumour. Another feature of interest in the Furuki study is the site of the recurrence. In each case, the recurrence was at the periphery of the regenerated bone, and not at the original margin of the lesion, or in adjacent cancellous bone.

Marks *et al* (1983) suggested that a preoperative computed tomography scan is an important part of the diagnostic armamentarium as it allows the surgeon better to establish the boundaries of the tumour and determine if the lesion extends beyond bone into the soft tissues.

(g) Macroscopic Features

Upon removal of the lesion, whether in total or piecemeal, it is important for the surgeon and pathologist to examine both the inside and outside of the cyst sac, as this may reveal important diagnostic clues (Philipsen and Reichart, 1998). The luminal surface of the sac may show one or several polypoid or papillomatous, pedunculated, exophytic masses. This subtype of unicystic ameloblastoma has been named intracystic, luminal, intraluminal, or mural ameloblastoma, and corresponds to the plexiform unicystic ameloblastoma (as termed by Gardner, 1981).

In addition to these intraluminal protruberances, the inside of the cyst may show one or several rounded and only slightly protruding nodules that in fact may also be viewed from the outside of the cyst wall. These formations are termed mural or intramural nodules and result from infiltrating and invading islands of ameloblastoma tissue. Philipsen and Reichart (1998) suggested the terms intraluminal unicystic ameloblastoma and intramural unicystic ameloblastoma for lesions displaying the protruberances and nodules respectively. The former term precisely indicates the location of the tissue proliferation.

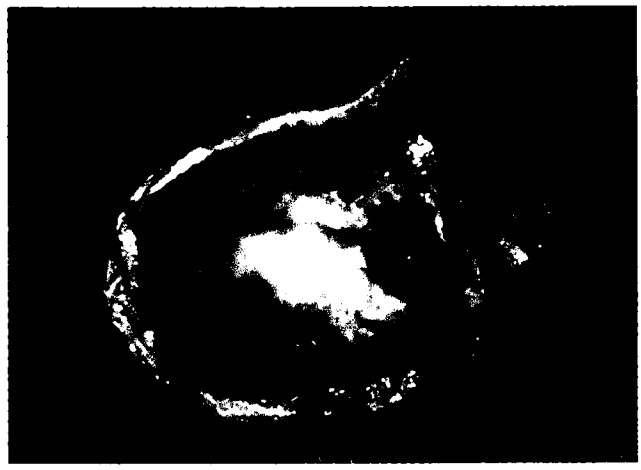

Figure 3: Bisected gross specimen of a simple unicystic ameloblastoma.

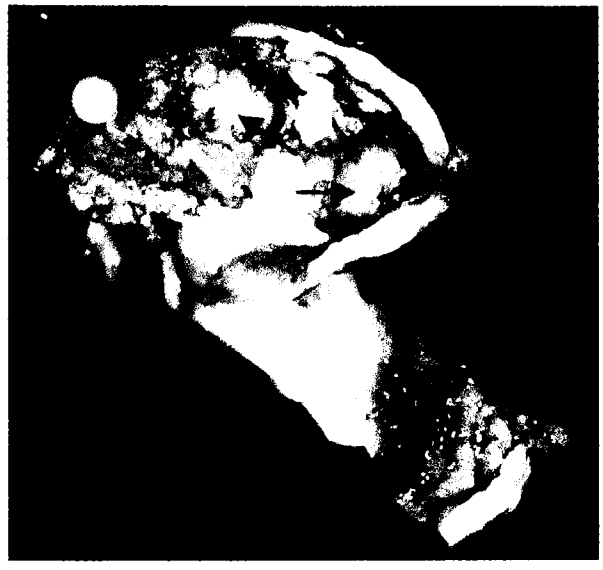

Figure 4: Opened gross specimen of a unicystic ameloblastoma showing intraluminal protruberances (indicated by arrows) – a so–called intraluminal unicystic ameloblastoma.

Figure 5: Opened gross specimen of a unicystic ameloblastoma showing intramural nodules (indicated by arrows) – a so–called intramural unicystic ameloblastoma.

(h) ***Histological Features***

Vickers and Gorlin (1970) studied 'ten examples of cystic lesions of the jaws that manifested a distinctly altered epithelial lining.' The histologic changes noted in this material were compared with published photomicrographs of early ameloblastomas, mural ameloblastomas, or examples of ameloblastoma arising in association with 'dental' cysts. They noted the following features which have since become established as the histological criteria for diagnosis of an ameloblastoma and are often referred to as the Vickers–Gorlin criteria.

These epithelial features were:

- hyperchromatism of basal cell nuclei of the epithelium lining the cystic cavities;
- palisading of the basal cells with polarization, sometimes referred to as reverse polarization, of the basal cell nuclei;
- cystoplasmic vacuolation of basal cells;
- marked intercellular spacing;
- homogenization or hyalinization of a thin, band–like area of fibrous tissue adjacent to the epithelium;
- bud–like proliferations of the basal layer; and
- epithelial nests seemingly detached from the extensions.

Hyperchromatism, palisading with polarization, and cytoplasmic vacuolation were constant histopathologic features of these cystic lesions. No feature appeared more significant and all three of these criteria should be present for the diagnosis of ameloblastoma.

Hyperchromatism of basal cell nuclei of the epithelium lining of the cystic cavities was observed in each of the ten specimens. It was apparent with low power examination and was photomicrographically reproducible (Vickers and Gorlin, 1970).

Palisading with polarization of basal cell nuclei of the epithelium lining the cystic cavities was observed in nine of ten specimens, with the exception being considered too small to be representative. Palisading is the term used to describe the orderly arrangement of epithelial cells with their long axes orientated at right angles to the basement membrane. Polarization, or reverse polarization, is a term describing the apparent movement of cell nuclei, away from the basement membrane. When observed together palisading and polarization of cell nuclei were considered noteworthy (Vickers and Gorlin, 1970).

Cytoplasmic vacuolation of basal cells of the epithelium lining the cystic cavities was observed in all but one specimen, the inadequate one. Cytoplasmic vacuolation was readily observed and was most prominent in that portion of the cell approximating the basement membrane. Intercellular spacing was also marked and suggested the possibility that an 'unidentified substance' was present between the cells. When cytoplasmic vacuolation and intercellular spacing occurred together and when they were most notable in basilar and parabasilar areas of the epithelium, they were considered noteworthy (Vickers and Gorlin, 1970).

The other histologic features of homogenization or hyalinization of a uniform, thin, band–like area of fibrous connective tissue adjacent to the epithelium, and bud–like proliferation of the epithelial lining were seen in six of the ten specimens. Epithelial nests, seemingly detached from the extensions, demonstrating histologic features of hyperchromatism, palisading with polarization, and cytoplasmic vacuolation with intercellular spacing, were also seen (Vickers