Differential diagnosis of dentigerous cyst-like lesions: Clinico-pathologic features of 63 cases

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SUMMARY

A series of unilocular pathological conditions resembling dentigerous cysts was analyzed and the clinical and radiographic features correlated with the microscopic diagnosis. The most common lesions were found to be true dentigerous cysts followed by unicystic ameloblastomas and odontogenic keratocysts. Unicystic ameloblastomas with a dentigerous cyst-like appearance occurred most frequently in the mandibular third molar region and commonly caused expansion of the mandible. The adjacent teeth in these cases showed a high occurrence rate of root resorption. Unlike the site distribution of true dentigerous cysts reported in other series, 50 per cent of our cases occurred in the maxillary anterior and premolar regions. Our study emphasizes the importance of microscopic examination of all pericoronal cystic lesions.

OPSOMMING

Die kliniese- en radiologiese beeld van 63 gevalle van unilokulêre patologiese toestande wat tandhoudende siste naboots, is vergelyk met die mikroskopiese diagnose. Die mees algemene toestand wat voorgekom het, was tandhoudende siste, gevolg deur unisistiese ameloblastoom en odontogene keratosiste. Unisistiese ameloblastome met die radiologiese beeld van 'n tandhoudende sist, het mees algemeen in die mandibulêre derde molaar area presenteer en het dikwels beenekspansie veroorsaak. Die aangrensende tande het 'n hoë frekwensie van eksterne wortelresorpsie getoon. Anders as in ander reekse, het 50 persent van tandhoudende siste in die maksillêre anterior en premolaar areas voorgekom. Hierdie studie beklemtoon die belang van mikroskopiese ondersoek van alle perikoronale sisteuse letsels.

INTRODUCTION

A dentigerous cyst is defined as a unicystic cavity which encloses the crown of an unerupted tooth by expansion of its follicle and is attached to the neck of the tooth (Shear, 1992). In a radiographic context, a radiolucent area surrounding the crown of an unerupted tooth may be seen with odontogenic keratocysts of the envelopmental or follicular variety as well as unicystic ameloblastomas involving adjacent unerupted teeth, and these may be misinterpreted as dentigerous cysts. This could have prognostic consequences as the recurrence rates of the various pathologic lesions that envelop the crown of a tooth vary significantly. Simple enucleation is an adequate form of treatment for dentigerous cysts but more extensive surgery is required for unicystic ameloblastomas and odontogenic keratocysts. Even with adequate treatment, the recurrence rates of unicystic ameloblastomas and keratocysts are reported to be high

(Vedtofte and Praetorius, 1979; Ueno *et al.,* 1986). Accurate diagnosis of jaw cysts is therefore essential for adequate treatment planning.

The purpose of this study was to appraise the clinico-pathologic features of pericoronal radiolucencies resembling dentigerous cysts.

MATERIAL AND METHODS

Sixty three lesions with a radiologic appearance of a dentigerous cyst were retrieved from the files of the department of Maxillo-Facial and Oral Surgery at the Medical University of Southern Africa. This hospital is a reference centre for the Northern Transvaal region and all patients in the study are Black and mostly of rural origin. The radiologic appearance with special reference to the size (longest axis measured on panoramic radiograph) and location of the lesion, the presence or absence of root resorption of adjacent teeth, expansion of cortical plates and displacement of the associated tooth, was compared with the age, sex and microscopic diagnosis of the lesion.

RESULTS

Sixty-three unilocular paracoronal cystic lesions resembled dentigerous cysts radiologically. The histological diagnosis of these lesions are listed in

Fig. 1: Unicystic ameloblastoma with root resorption of the associated teeth.
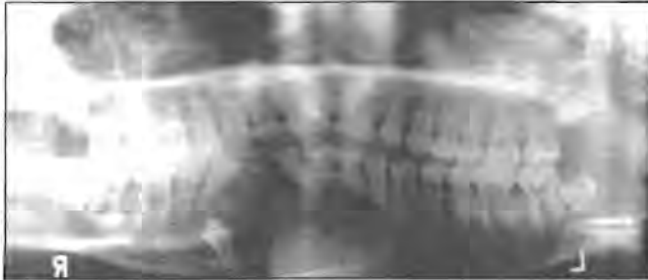

Fig. 2: Adenomatoid odontogenic tumour causing tooth displacement and root resorption.

Fig. 3: Unicystic ameloblastoma of the left mandible showing enlargement in all dimensions.

Fig. 4: Dentigerous cyst of the mandible showing enlargement along the medullary space.

Fig. 5: Calcifying odontogenic cyst of the mandible associated with an impacted canine and exhibiting mural calcifications (arrows).

Fig. 6: Multiple keratocysts involving the left and right mandibular ramus and right globulomaxillary area in a patient with the naevoid basal cell carcinoma syndrome.

panoramic radiograph and the presence of root resorption and tooth displacement are shown in Table I.

Unicystic ameloblastomas showed an equal sex distribution, while dentigerous cysts, odontogenic keratocysts and calcifying odontogenic cysts were more common in males. Adenomatoid odontogenic tumours were found in females only. The mean age at presentation of the six cyst types were not found to differ significantly. The mean size of the unicystic ameloblastomas were significantly larger than the odontogenic keratocysts and dentigerous cysts ($p < 0,005$) while odontogenic keratocysts' mean size were significantly larger than that of dentigerous cysts ($p < 0,05$). Root resorption was most frequently observed in unicystic ameloblastomas (64 per cent of cases) (Fig. 1) and calcifying odontogenic cysts (60 per cent of cases). Displacement of non-involved teeth was a constant finding in cystic adenomatoid odontogenic tumours (Fig. 2). The enlargement of unicystic ameloblastomas occurred in all dimensions and frequently caused bony expansion (Fig. 3). Enlargement of follicular and odontogenic keratocysts in the mandible appeared to follow the medullary space initially (Fig.4) with bony expansion seen only in the largest examples.

All paradental cysts were associated with partially erupted third molars. Six cystic adenomatoid odontogenic tumours occurred in the maxilla and one in the mandible. One very large lesion of the latter type extended across the maxillary midline. Three calcifying odontogenic cysts presented in the maxilla and two in the mandible. One cyst in each jaw showed radiographic evidence of calcifications (Fig. 5).

Thirteen dentigerous cysts were located in the maxilla, the majority of which were associated with impacted central incisors (4 cysts), canines (2 cysts) and premolars (4 cysts). In the mandible, only 3 dentigerous cysts involved third molars; one, a second molar, while two involved canines. One dentigerous cyst was associated with a primary maxillary canine. Eight odontogenic keratocysts were located in the mandibular (7 cases) or maxillary (one case) third molar areas and 5 presented in the canine region (3 maxillary and 2 mandibular). Two patients presenting with the basal cell nevus syndrome had multiple cysts

Table I. Three of the calcifying odontogenic cysts with a dentigerous cyst-like appearance were subclassified according to Praetorius *et al.,* (1981) as type IA, and one each as type IB and IC respectively. The sex distribution, mean age at presentation, average size of the cyst as measured on a

Table I: Clinical data.

	n	Sex Male	Sex Female	Mean Age (SD)	Mean Size in mm (SD)	Root Resorption	Tooth Displacement
Unicystic Ameloblastoma	14	7	7	15,5 ±6,3	80 ±22,7	9	5
Dentigerous Cyst	21	16	5	16 ±16,2	35 ±11,5	4	5
Odontogenic Keratocyst	13	10	3	15 ±12,5	45 ±20,1	1	3
Adenomatoid Odontogenic Tumour	7	0	7	12 ±3,9	45 ±15,7	1	7
Calcifying Odontogenic Cyst	5	4	1	23 ±7,0	40 ±6,5	2	3
Paradental Cyst	3	2	1	21 ±2,0	10 ±12,7	0	0

(Fig. 6). The unicystic ameloblastomas showed a predeliction for the mandibular third molar region (11 cysts) followed by the mandibular canine region (3 cysts). No unicystic ameloblastomas with a dentigerous cyst-like appearance occurred in the maxilla.

DISCUSSION

The importance of an accurate diagnosis of a lesion with a dentigerous cyst-like appearance, especially in a Black population sample in which dentigerous cysts are less common than in Whites (Shear, 1992), cannot be over emphasized. By the same token the presence of unicystic ameloblastomas must not be underestimated, being the second most common cystic lesion found in our patients. Outstanding characteristics of this potentially aggressive neoplasm is its large size when compared to the other cysts, its tendency to expand more symmetrically than other cystic lesion in the mandible as well as its common association with root resorption of adjacent teeth. Adenomatoid odontogenic tumours were found in females only but although the majority seem to affect the anterior maxilla, it also occurred in the mandible in one instance. Tooth displacement was more frequently observed in adenomatoid odontogenic tumours than in any of the other cystic lesions. Dentigerous cysts were more frequently encountered in the anterior maxilla and their most frequent association with impacted mandibular third molars (Shear, 1992) was not found in our study. The lower frequency of impacted third molars in Blacks (Brown et al., 1982) may account for this observation in our exclusively Black sample. The attachment of the cyst wall to the impacted tooth is reported to extend more apically in ameloblastomas than dentigerous cysts (Ikeshima et al., 1990). In large examples of dentigerous cysts the associated tooth is often rotated, making this measurement difficult to interpret on panoramic radiographs.

Our study does not support the report that there is a frequent occurrence of root resorption in association with dentigerous cysts (Struthers and Shear, 1976). The site distribution of odontogenic keratocysts in our study conform to that of another series (Shear, 1992). Forssell (1980) observed a relationship between the cyst and the crown of a tooth in 41 per cent of a series of 135 cases. McIvor (1972) however, demonstrated this relationship exclusively in the mandible. In our study,

4 maxillary odontogenic keratocysts presented in association with impacted teeth. The frequent association of odontogenic keratocysts with impacted teeth have led Altini and Cohen (1980) to introduce the term "follicular primordial cyst" for this group of lesions. They postulated that this association may arise following eruption of a tooth into a pre-existing cystic cavity in the same way as a tooth erupts into the oral cavity. Although we have no microscopic evidence, we believe that this hypothesis may be extended to all cysts in our series, except for the follicular and paradental cysts, in both of which types their association with an impacted tooth have been satisfactorily explained (Shear, 1992).

Although certain specific features seen on radiographs, such as the size of lesion, its location, the presence or absence of root resorption or tooth displacement and other factors such as age and sex of the patient may influence the clinical differential diagnosis, a thorough histological examination is essential in establishing an accurate diagnosis.

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A retrospective analysis of 367 cystic lesions of the jaw—the Ulm experience

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SUMMARY. Out of 846 cyst-like lesions of the jaws, 367 cases were retrieved from the files of the Department of Oral and Maxillofacial Surgery at the University of Ulm and classified according to the new World Health Organization's classification for odontogenic tumours and cysts. Radicular and residual cysts comprised 56.9%, dentigerous cysts 21.3%, odontogenic keratocysts 10.6%, unicystic ameloblastomas 4.1%, nasopalatine duct cysts 2.7%, glandular odontogenic cysts 1.6% and paradental cysts, traumatic bone cyst, calcifying odontogenic cyst and lateral periodontal cyst each less than 1% of the sample. Nearly one third of the specimens were obtained from military patients; despite an expected bias towards young males, unicystic ameloblastomas presented one and a half decades later than is generally reported.

INTRODUCTION

Before the recent adoption of the revised World Health Organization's classification of odonotogenic tumours and cysts (Kramer et al., 1992), epidemiological studies on cystic jaw lesions were difficult to interpret due to the omission of recently described entities, which had not been taken up in any classification system. Examples of these are the paradental cyst which arises from odontogenic epithelial residues stimulated into activity by inflammation (Craig, 1976) and the aggressive glandular odontogenic cyst, the exact origin of which is less clear (Shear, 1992). The calcifying odontogenic cyst, which is now classified as an odontogenic tumour, occurs both in neoplastic and cystic subtypes (Hong et al., 1991). Unicystic ameloblastomas are divided into three subtypes, a division which is based on the histological nature of its epithelial lining. Type I unicystic ameloblastomas exhibit a simple ameloblastic epithelial lining whereas Type II shows intraluminal proliferation and Type III mural invasion. The latter type is reported to be associated with a higher recurrence rate (Ackermann et al., 1988).

The purpose of this study was to revise and reclassify cystic lesions of the jaws diagnosed and treated in the Department of Oral and Maxillofacial Surgery, University of Ulm, over the last 5 years.

MATERIAL AND METHODS

The clinical examination forms and radiographs of all cystic lesions affecting the jaws were retrieved from the files of the Department of Oral and Maxillofacial Surgery at the University of Ulm, Germany. 367 out of 846 microscopic sections were supplied for re-examination by the Department of Pathology at the

Bundeswehrkrankenhaus Ulm as well as from the University Department. Only cases on which clinical information, a radiograph and representative microscopic sections where available, were included in the study. Each case was re-evaluated and classified independently according to the criteria set in the second edition of the World Health Organisations classification of jaw cysts and tumours (Kramer et al., 1992) by two oral pathologists.

RESULTS

367 cases were included in the study and 22 excluded due to a lack of radiographs and/or unrepresentative microscopic sections. Nearly one third of the cases
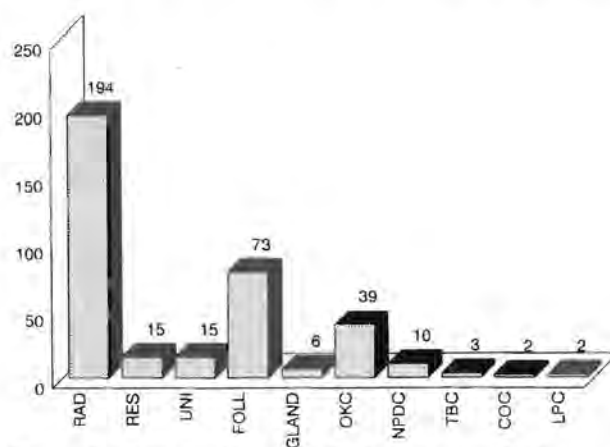

Fig. 1 – Distribution of jaw cysts. RAD – radicular; RES – residual; UNI – unicystic ameloblastoma; FOLL – follicular; GLAND – glandular odontogenic; OKC – odontogenic keratocyst; NPDC – nasopalatine duct cyst; TBC – traumatic bone cyst; COC – calcifying odontogenic cyst; LPC – lateral periodontal cyst.
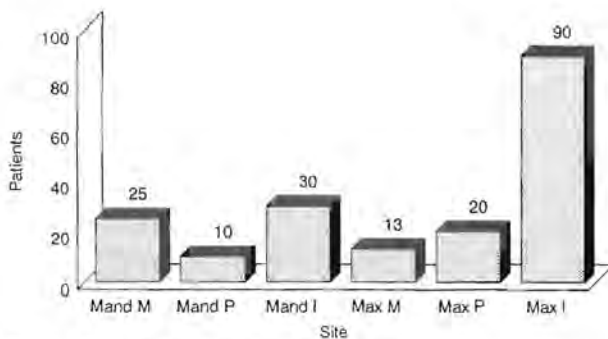
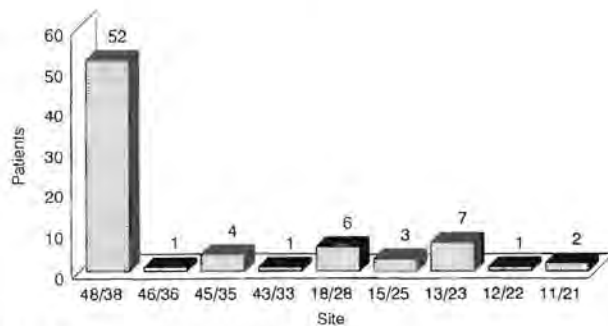**Fig. 2** – Site distribution of radicular cysts.

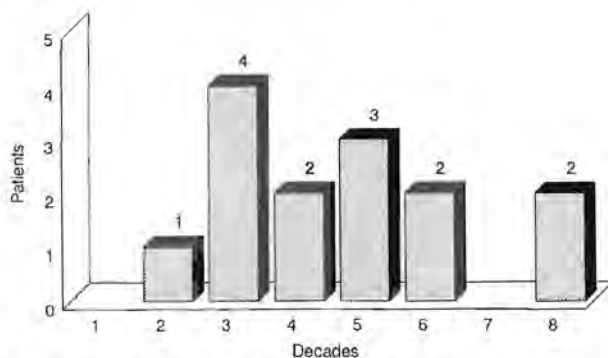**Fig. 3** – Site distribution of dentigerous cysts.

Fig. 4 – Age distribution of unicystic ameloblastomas.

recorded were military patients treated in the Bundeswehrkrankenhaus. The distribution of cystic jaw lesions in this study is reflected in Figure 1.

Radicular (n = 194) and residual cysts (n = 15) comprised 56.9% of lesions diagnosed. The mean age at presentation of radicular and residual cysts was 34.4 years (SD = 14.2) and 52.7 years (SD = 13.2) respectively. Radicular cysts occurred most commonly in the maxillary incisor region (Fig. 2).

Dentigerous cysts (n = 78) comprised 21.3% of the sample and presented at a mean age of 37.1 years (SD = 15.3 years). The mandibular third molars were most frequently involved (Fig. 3).

Three patients out of a total of 39 with odontogenic keratocysts, the latter comprising 10.6% of the sample, suffered from the basal cell naevus syndrome. The mean age at presentation of odontogenic keratocysts was 40.3 years (SD = 19.5 years) and the majority of cases (n = 21) involved the mandibular

molar area. In 10 of those cysts, X-ray examination showed teeth or rudiments inside the cavity which led to a primary misdiagnosis of dentigerous cyst.

Unicystic ameloblastomas (n = 15) comprised 4.1% of the sample and presented at a mean age of 40.7 years (SD = 18.8 years). The youngest patient was in the second decade of life whereas 2 cases presented in the eighth decade (Fig. 4). 8 unicystic ameloblastomas occurred in the mandibular molar area, 6 of which appeared radiographically as dentigerous-like cysts, and 4 lesions affected the maxilla. 13 unicystic ameloblastomas were lined by non-invasive odontogenic epithelium (Type I) and 2 cases exhibited foci of mural invasion (Type III).

The mean ages at presentation of nasopalatine duct cysts (n = 10, 2.7% of the sample) and glandular odontogenic cysts (n = 6, 1.6% of the sample) were 44.9 years (SD = 13.5 years) and 46 years (SD = 14.3 years) respectively. The paradental cyst (n = 3), traumatic bone cyst (n = 3), calcifying odontogenic cyst (n = 2) and lateral periodontal cyst (n = 2) each contributed to less than 1% of the sample. No examples of gingival cysts of infants and adults, eruption cysts and nasolabial cysts were found in this study.

DISCUSSION

Accurate diagnosis of cystic lesions of the jaw is crucial as various types are aggressive and may lead to local recurrence if incorrectly diagnosed and inappropriately treated. Many cystic lesions of the jaw share clinical and radiographic features and microscopic examination forms an important part of the diagnostic process. For this purpose, an in-depth knowledge of an internationally accepted classification system, such as that proposed by the World Health Organization (*Kramer* et al., 1992) is essential.

The description of new cyst entities in combination with the new WHO-classification on the one side and improbable lack of diagnosed ameloblastomas on the other prompted this retrospective investigation. It shows the incapability of a general pathologist to make a correct and specific diagnose of jaw cysts and necessitates cooperation with an experienced oral pathologist.

Due to their association with the ghost cell odontogenic tumour, the calcifying odontogenic cyst is no longer grouped amongst cysts in this classification but is classified as a benign tumour originating from the odontogenic apparatus. This cystic tumour, as well as the odontogenic keratocyst (*Brown*, 1970; *Niemeyer* et al., 1985), unicystic ameloblastoma (*Ackermann* et al., 1988) and glandular odontogenic cyst (*Patron* et al., 1991), are notorious for their aggressive behaviour and high recurrence rates (*Machtens* et al., 1972). This implies that in the present study, 17% of the total sample of cystic jaw lesions, required more than simple enucleation as a curative surgical procedure. Type III unicystic ameloblastomas, of which 2 cases were diagnosed in this study, exhibit infiltrative features and should be treated

similarly to the polycystic types, with wide excision or even resection of the involved jaw segment (*Acker-mann* et al., 1988). These results have induced a recall of those patients with diagnosed aggressive cysts or ameloblastomas in order to prove the necessity for further treatment.

A large percentage of patients in this study were military personnel and our data is probably biased towards young males. The high mean age of 40.7 years for unicystic ameloblastomas was therefore surprising as these cystic tumours are reported to occur most frequently in the first half of the third decade (*Robinson* and *Martinez*, 1977; *Gardner*, 1981; *Acker-mann* et al., 1988). As no literature is available on unicystic ameloblastomas in the German population, this finding may point towards an older age incidence for unicystic ameloblastomas in Germany. Unicystic ameloblastomas frequently involved the mandibular molar area where impaction of a mandibular third molar in the cyst wall was common. Unless these lesions are examined microscopically, they will be misdiagnosed as dentigerous cysts.

The frequency of the different cyst types encountered in this study, as well as the sites of involvement of radicular, residual, dentigerous and odontogenic keratocysts and unicystic ameloblastomas, are in agreement with the recent literature (*Shear*, 1992). The lack of examples of gingival cysts of infants and adults and eruption cysts, as well as the infrequent occurrence of paradental cysts is the result of exclusion of all cases without a microscopic diagnosis. Most of these lesions either go unnoticed or are not submitted for microscopic examination after removal and are probably more common than is reflected in a study of this nature.

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Scientific Article

Wetenskaplike Artikel

Clinico-pathological study of 30 unicystic ameloblastomas

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SUMMARY

The clinico-pathological records of 30 unicystic ameloblastomas collected over a period of 10 years were studied. The mean age at diagnosis was 18,0 years (SD ±8,1), most lesions were located in the mandible and were frequently associated with impacted teeth, root resorption and tooth displacement. The unicystic ameloblastomas in 11 patients (4 females and 7 males) exhibited invasion of the fibrous wall, 4 cases (1 female and 3 males) showed intra-luminal proliferation and the remaining 15 specimens (9 females and 6 males) were lined by non-proliferating ameloblastic epithelium. Two cases recurred 3 and 7 years after initial surgical removal. This study reveals the potential aggressive behaviour of unicystic ameloblastomas and underlines the importance of a thorough microscopic examination for sub-classification.

OPSOMMING

Die klinies-patologiese rekords van 30 unisistiese ameloblastome, wat oor 'n tydperk van 10 jaar versamel is, is bestudeer. Die gemiddelde ouderdom by diagnose was 18,0 jaar (SD ±8,1). Die meeste letsels was in die mandibula en was met geïmpakteerde tande, wortelresorbsie en tandverplasing geassosieer. In 11 pasiënte (4 vroulik, 7 manlik) het die unisistiese ameloblastome die fibreuse wand binnegedring, in 4 gevalle (1 vroulik, 3 manlik) was intraluminale proliferasie teenwoordig en in die oorblywende 15 gevalle (9 vroulik, 6 manlik) was die sist deur 'n nie-prolifererende ameloblastiese epiteel. In twee gevalle het herhaling onderskeidelik 3 en 7 jaar na die aanvanklike chirurgiese verwydering voorgekom. Hierdie studie bevestig die potensiële aggressiewe gedrag van unisistiese ameloblastome en beklemtoon die noodsaaklikheid van deeglike mikroskopiese ondersoek vir subklassifikasie.

INTRODUCTION

The unicystic ameloblastoma is a unilocular, cystic epithelial odontogenic tumour initially described by Robinson and Martinez in 1977. Males and females are affected approximately equally. The lesions usually occur in the mandible and especially in the molar-ramus area, while the maxilla is only occasionally affected (Ackerman, Altini and Shear, 1988). They usually occur in the second to fourth decades and the mean age at the time of diagnosis is reported to be 23,8 years. The lesions appear radiologically as a well defined unilocular radiolucency of varying size (Ackermann et al., 1988). When associated with an unerupted tooth, the appearance closely resembles a dentigerous cyst. Involvement of the roots of teeth may give it a radicular cyst-like appearance (Lucas, 1984) and in many cases can only be distinguished from odontogenic keratocysts by microscopic examination. Unicystic ameloblastomas are divided into three groups. Group 1 include the simple cystic lesions lined by an epithelium that does not infil-

trate into the fibrous cyst wall. Lesions in Group 2 show intra-luminal epithelial proliferation and the epithelium in Group 3 lesions invade the fibrous cyst wall. Group 1 and 2 lesions may be treated by enucleation, whereas Group 3 lesions should be treated more radically to prevent recurrences (Ackermann et al., 1988).

As a rule unicystic ameloblastomas behave more aggressively than other odontogenic cysts. It is important therefore to recognise the clinical features which may facilitate an accurate diagnosis of the condition. This study was undertaken to determine the clinico-pathological features of unicystic ameloblastomas in a rural black population.

MATERIALS AND METHODS

Microscopic sections of all unicystic lesions that were biopsied between 1982 and 1992 at Medunsa were retrieved and re-evaluated. The unicystic ameloblastomas were subdivided into three groups using the criteria of Ackermann et al., 1988. Clinical data and radiographs were obtained from patient files. The site of occurrence was designated as molar-ramus, premolar or incisor according to the centre of the radiolucent lesion on a panoramic radiograph.

RESULTS

Thirty cases were diagnosed as unicystic ameloblastoma, 16 were males and 14 females. The mean age of the patients was 18,0 years (SD =±8,1) (range 8-43 years) and 63,3 per cent occurred in the second decade (Fig. 1). Twenty seven of the lesions were present in the mandible and only 3 in the maxilla (Fig. 2). The lesions varied in size from 2,5-12 cm mesio-distally and 22 of the lesions were more than 5 cm in diameter on the panoramic radiographs. One mandibular tumour was associated with a pathological fracture.

Radiologically, 11 of the lesions were associated with impacted teeth (Fig. 3), 13 with root resorption, 15 with tooth displacement and 8 with tooth displacement and root resorption. The impacted teeth associated with the lesions were mainly the mandibular third molars (n=7), followed by mandibular second molars (n=3) and mandibular canines (n=2). Two of the 3 maxillary lesions presented in the "globulo-maxillary" area. Of the 14 lesions in females, 9 were classified as Group I (Fig. 4), 1 as Group II (Fig. 5) and 4 as Group III. There were 6 Group I lesions and 7 Group III lesions amongst the 16 males, the remaining 3 were Group II lesions (Fig. 6).

In 7 unicystic ameloblastomas, 50 per cent or more of the lining was a nondescript type of epithelium (Fig. 7). Three out of 4 Group III lesions had a plexiform intra-luminal proliferation, the other had multiple mural nodules projecting into the lumen (Fig. 8). Inflammation in 3 lesions was associated with extensive epithelial arcading and 4 showed sub-epithelial hyalinization. Two cases recurred as polycystic ameloblastomas 3 and 7 years after surgical treatment respectively. The ‌ was originally classified as Group III (Fig. 9), whereas the other case was a Group I unicystic ameloblastoma.

DISCUSSION

Since the original description of unicystic ameloblastoma (Robinson and Matinez, 1977) various reports on the aggressive behaviour of this cystic lesion have appeared (Ackermann *et al.*, 1988; Gardner, Morton and Worsham, 1987; Kahn, 1989; Keszler and Dominques, 1986; Punnia-Moorthy, 1989). Two patients in our study, which extends over a period of 10 years, presented 3 and 7 years after initial surgery with recurrences. Both recurrences exhibited the growth pattern of a polycystic ameloblastoma. Although Ackermann *et al.*, (1988) propose a more radical form of treatment for Group III lesions, a Group I lesion recurred in our study and this emphasizes the potentially aggressive behaviour of all unicystic ameloblastomas and
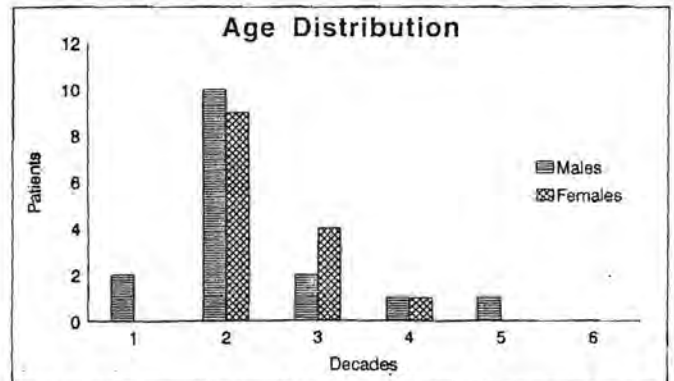

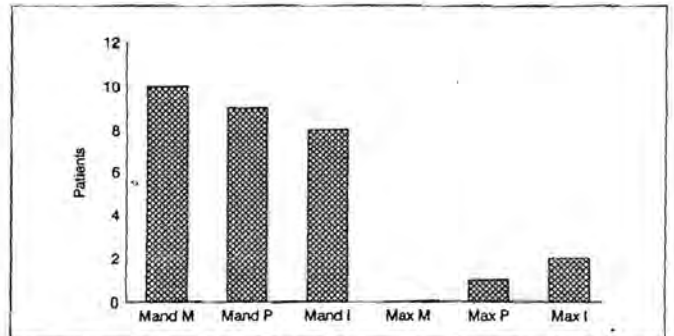Fig. 1: The histogram of the age distribution of males and females.

Fig. 2: The site distribution of 30 unicystic ameloblastomas. Mand=mandibular, Max=maxilla, M=molar ramus area, P=premolar area, I=incisor area.
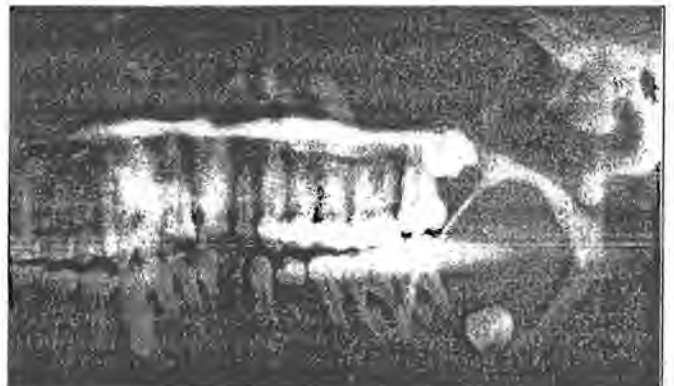

Fig. 3: Panoramic radiograph of an unicystic ameloblastoma associated with an impacted mandibular third molar.

Fig. 4: Section through a resected mandible with a microscopically confirmed Group I lesion. Note the simple unicystic cavity.

Fig. 5: Cross section through a microscopically confirmed mandibular Group II lesion. Note the intra-luminal proliferation (arrow).
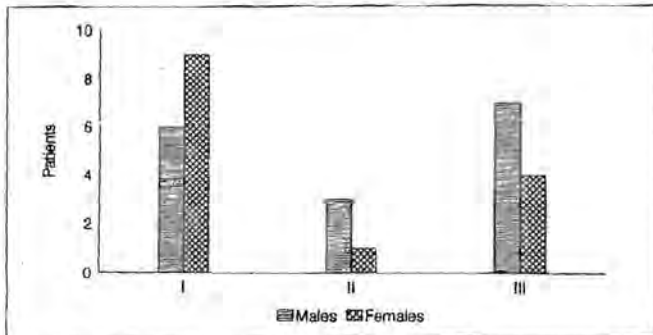

Fig. 6: The histogram of the different groups for females and males.
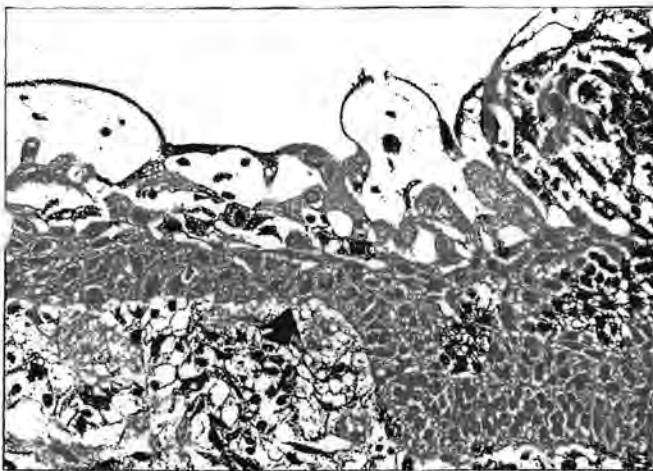

Fig. 7: Photomicrograph of a Group I lesion. Note the nondescript epithelium (left) and the sharp transition (arrow) to typical ameloblastic epithelium. (HE, X300).

Fig. 8: The lining of a Group II lesion showing an intra-luminal nodular proliferation (HE, X100).
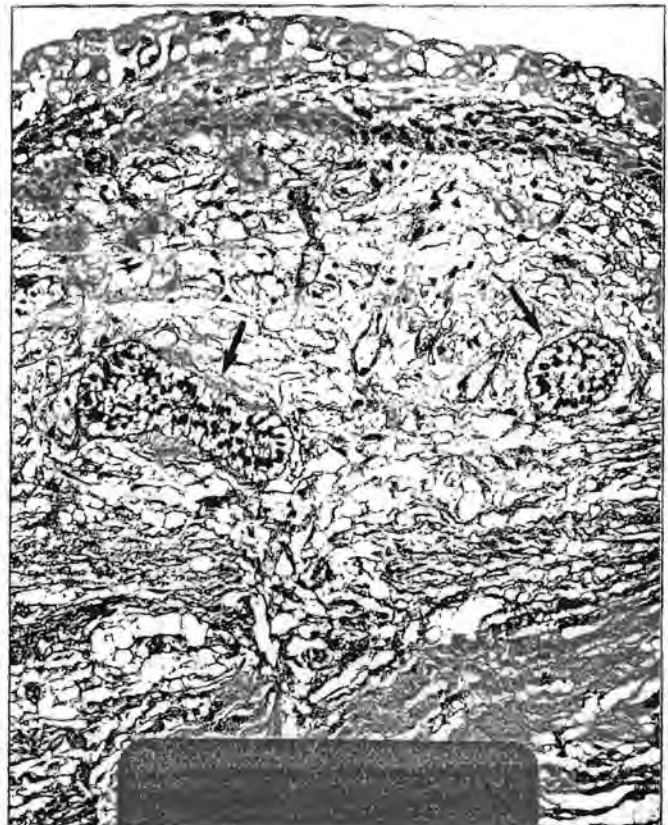

Fig. 9: The lining of the Group III lesion that recurred. Note the islands of ameloblastic epithelium in the connective tissue wall (arrows). (HE, X180).

highlights the importance of complete surgical removal. This recurrence may, on the other hand, reflect an inherent weakness in the proposed sub-grouping of unicystic ameloblastomas. If the whole cyst wall is not examined microscopically, an exercise which is highly impractical if not impossible in larger examples, mural invasion cannot be excluded categorically. The diagnosis of an unicystic ameloblastoma on a small biopsy specimen is not

recommended. Moreover, the frequent occurrence of nondescript epithelium and inflammation may mask the typical characteristics of the ameloblastic epithelial lining. This microscopic sub-classification of unicystic ameloblastomas should therefore not be attempted on anything less than a thorough microscopic examination of the whole cyst wall. After such an examination the number of lesions placed in Group III would probably increase.

Our study supports the finding that there is an equal sex distribution for the unicystic ameloblastoma as well as a tendency for it to occur in young patients. Our cases however, presented on average 6 years earlier than those of Ackermann *et al.*,

(1989), probably because patients were seeking treatment sooner and had easier access to the hospital in the years 1981-1991. Most tumours occurred in the mandible and maxillary involvement was less common. A large number of mandibular lesions could be easily mistaken for dentigerous cysts, because of their association with impacted molars and canines. This is related further to the frequent occurrence of root resorption, a feature often found in dentigerous cysts (Shear, 1992). In order to establish a correct diagnosis, microscopic examination of all cystic jaw lesions is mandatory.

Group I lesions predominated in our study and then followed Group III and lastly Group II unicystic ameloblastomas. This is in contrast to Ackermann's 1988 study in which Group III lesions were most frequent. The ratio between female and male in Group I lesions was 1,5:1 and in Group III lesions ·1,75. The significance of this finding is not known.

It is important to note that all unicystic ameloblastomas, irrespective of grouping, are neoplastic in nature and will recur if incompletely removed.

Although limited evidence is available on recurrences of unicystic ameloblastomas, it appears as if the latter may present either as a regrowth of the original unicystic lesion or as a multicystic ameloblastoma.

ACKNOWLEDGEMENT

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Serving Dentistry — ISO TC106

The 30th meeting of the International Standards Organisation's Technical Committee took place in Ottawa, Canada from 10-15 October 1994.

The countries represented were Australia, Brazil, Canada, China, France, Germany, Hong Kong, Italy, Japan, Netherlands, Norway, South Africa, Switzerland, Sweden, Thailand, United Kingdom and USA. The new South African flag was given a place of honour at the centre of the display seen in our photograph, which was taken at the conclusion of the opening ceremony. **Dr John Stanford**, Chairman of the Committee since 1991 is seen in the front of the picture with his predecessor, **Prof Pierre Laplaud** (1982-1990). the South African Bureau of Standards is a Participating Member of the Committee and Dr Heydt was their representative at the meeting. A detailed report on the work of the Committee will appear in a forthcoming issue of the *JOURNAL*.

Detection of human papillomavirus DNA in an ameloblastoma using the in situ hybridization technique

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Van Heerden WFP, van Rensburg EJ, Raubenheimer EJ, Venter EH: Detection of human papillomavirus DNA in an ameloblastoma using the in situ hybridization technique.

HPV type 18 DNA was identified in an intrabony ameloblastoma using radio-labelled in situ hybridization. The viral DNA was found in a verrucous lesion in a cystic area of the tumor. The absence of HPV DNA in other epithelial areas of the ameloblastoma is suggestive of a secondary infection. HPV is not considered to be an etiological factor in the pathogenesis of this ameloblastoma.

Human papillomaviruses (HPVs) are DNA viruses that infect only squamous epithelium at selected locations in the skin and mucosa. The virus usually infects the basal cell layers and viral DNA are observed in low copy numbers in these cells. An increase in copy numbers of replicating viral DNA are found in the more differentiated epithelial cells while production of viral particles is restricted to the fully differentiated superficial epithelial cells (1). Since this state of differentiation has not yet been achieved in culture, it has not been possible to reproduce HPV in the laboratory to study their natural life cycle (2). These viruses induce papillomatous, hyperplastic or verrucous lesions depending on the site of infection and the HPV type implicated. HPV involvement in upper respiratory and digestive tract lesions like focal epithelial hyperplasia, squamous cell papillomas, laryngeal papillomas, leukoplakia and squamous cell carcinoma has been demonstrated by means of immunohistochemical, DNA hybridization and polymerase chain reaction studies (2–6). More than 60 types of HPV have been isolated to date, of which types 1, 2, 4, 6, 7, 11, 13, 16, 18, 32 and 57 were found in the different oral lesions (7).

The association between HPV and odontogenic tumours and cysts has not

been studied to a great extent. HPV 16 DNA has been demonstrated in an odontogenic keratocyst using Southern blot hybridization (8), while KHAN found HPV capsid antigen in 3 out of 10 ameloblastomas in young persons (9). The purpose of this study was to investigate an ameloblastoma with typical HPV histologic changes for HPV DNA using the in situ hybridization technique. This is a sensitive technique and has the advantage of localizing viral DNA in tissue sections to the extent of detecting them at the resolution of single cells.

Material and methods

A 25-yr-old man reported to the Maxillofacial and Oral Surgery clinic complaining of a painless, bony hard swelling in the anterior mandible. Examination showed a tumor extending from the right mandibular angle to the contralateral first molar region. Expansion of the lingual and buccal cortices was evident with thinning and erosion of the buccal cortex in the right premolar area. Radiographs showed a well-circumscribed, multilocular lesion with root resorption of the associated teeth. No signs of mucosal ulceration were present.

After an incisional biopsy, a diagnosis of a follicular ameloblastoma was

made and the tumor was resected through an intraoral approach. The specimen was fixed in 10% buffered formalin for pathologic examination.

Macroscopic examination showed a gray-white solid tumor with cystic areas of varying size. A papillomatous lesion presenting as a luminal growth was present in one cyst. Microscopy revealed a follicular ameloblastoma with acanthomatous as well as granular cell differentiation (Fig. 1). The papillomatous lesion showed verrucous hyperplasia with hyperparakeratosis, elongation of the rete-ridges and groups of koilocytes lying in the upper part of the epithelium. These features resembled those of a verruca vulgaris (Fig. 2).

The biopsy material containing the papillomatous lesion, as well as blocks exhibiting the characteristic ameloblastomatous epithelium and including areas of granular cell and acanthomatous differentiation, were examined for the presence of HPV antigen using an ABC immunoperoxidase kit for the HPV group specific antigen (Lipshaw Corporation, Detroit) as well as in situ hybridization.

For HPV typing, the specific DNA probes of HPV 2, 6, 7, 11, 13, 16, 18 and 30 cloned in either pBR322 or pUC19 were used (kindly provided by Dr E-M de Villiers, Human Papillomav-
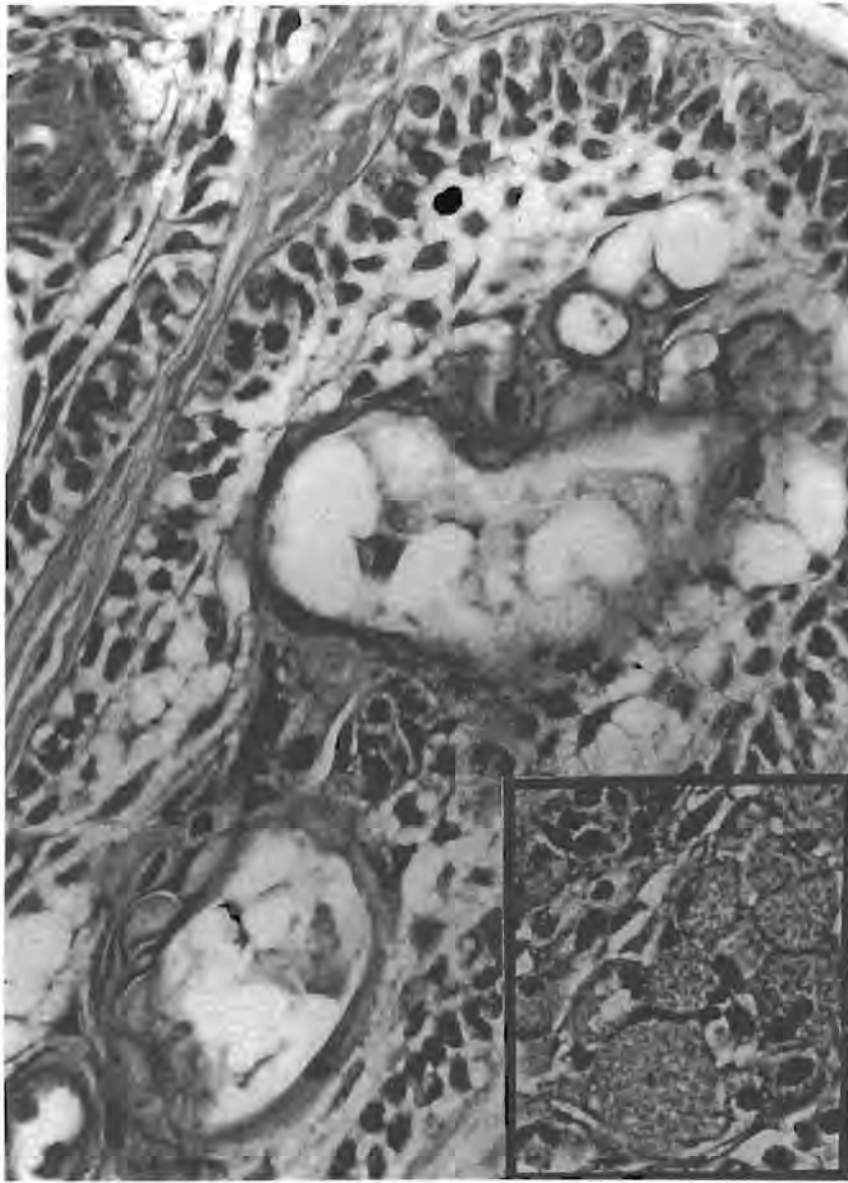
Fig. 1. Follicular ameloblastoma with central acanthomatous differentiation. HE × 200. *Inset.* Areas of granular cell differentiation. HE × 200.

irus Reference Centre, DKFZ, Heidelberg, Germany). The probes were labelled with ^{32}p dCTP using the multiprime DNA labelling system (Amersham, U.K.). The labelled probes had a specific activity of $2–5 \times 10^8$ counts/min/μg of DNA. For in situ hybridization 5–10 ng of each probe was used on individual sections.

pBR322 and pUC19 vectors served as negative control probes. Two paraffin embedded tissue sections (a cervical intraepithelial neoplasia and vulvar carcinoma positive for HPV 6 and 16 respectively) were used as positive control slides.
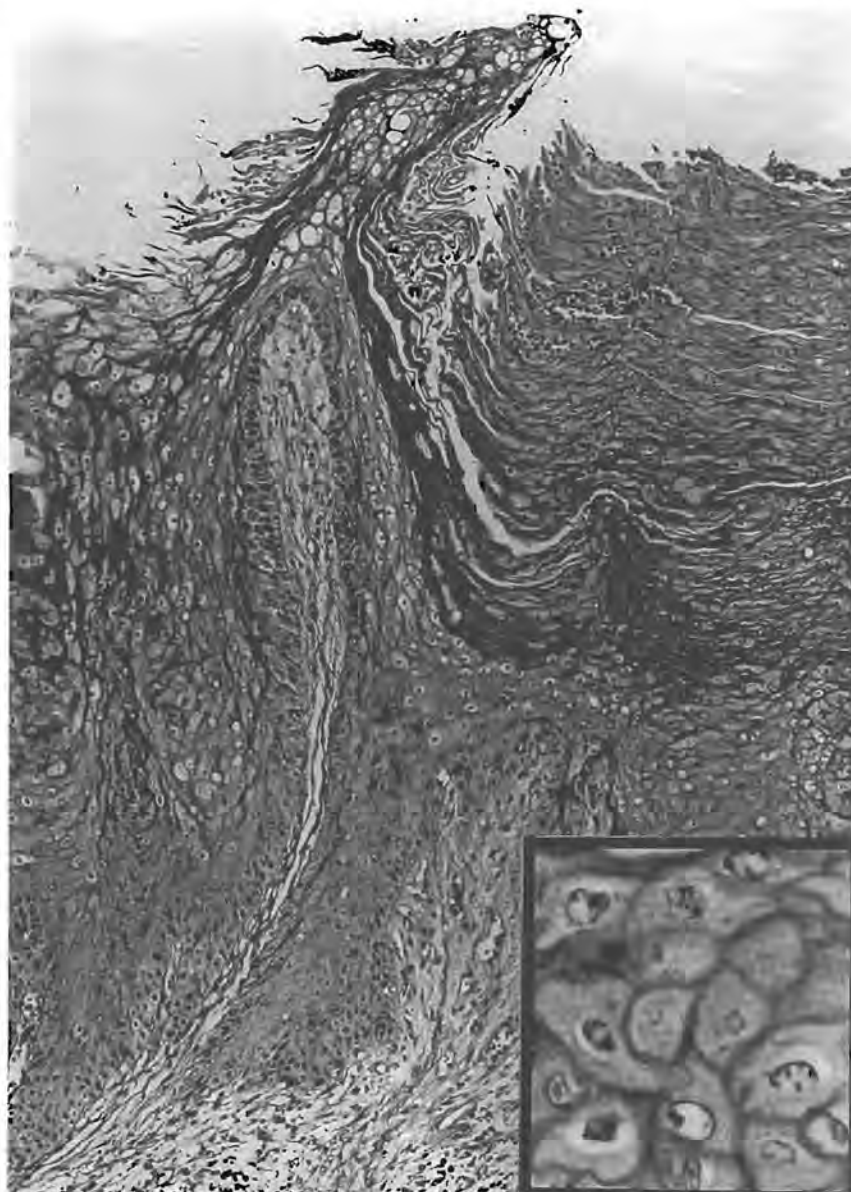
The tissue sections were incubated at 60°C overnight using 3-aminopropyl-triethoxysilane coated slides (10). Slides were deparaffinised and rehydrated by sequential immersion into xylene (3×10 min) and ethanol. They were then incubated in 0.2 N HCl for 20 min at room temperature and transferred to $2 \times SSC$ at 70°C for 10 min. The tissue sections were digested with a $2 \times SSC$, 0.1% SDS buffer solution containing Proteinase K (Boehringer, Mannheim, Germany) at a concentration of 0.01 μg/ml at 37°C for 30 min. Sections were post-fixed for 5 min in 4% paraformaldehyde, $2 \times SSC$ and 5 mM $MgCl_2$; 5 min in 50% formamide, $2 \times SSPE$ and acetylated (2×5 min). The slides were prehydridised (50% formamide, 10% dextran sulfate, $2 \times SSPE$, 100 mM glycin, 0.1% SDS, 2% $50 \times$ Denhardts, 10 mM Tris pH 7.4 and 200 μg/ml salmon sperm DNA) for 30 min at 52°C prior to the application of the probe solution. Heat-denatured probe solution (either HPV 2, 6, 7, 11, 13, 16, 18 or 30) was added to each section and slides were incubated for 16 hours at 52°C in a humidified chamber.

Following hybridisation, the slides were washed twice in a $2 \times SSPE/50\%$ formamide solution and once in 50% fomamide, 0.1% SDS, $2 \times SSC$, each wash for one hour at 37°C. Slides were dehydrated through graded ethanols containing 0.3 M NH_4 acetate. Slides were dipped in LM-1 emulsion (Amersham, UK), following instructions of the manufacturer. After exposure, slides were developed, fixed and counterstained with hematoxylin-eosin. The presence of HPV DNA sequences in the lesions was indicated by the condensations of black silver grains superimposed on the nuclei of cells.

Fig. 2. Micrograph of the papillomatous lesion showing parakeratosis, epithelial papillary processes and elongation of rete-ridges. HE × 100. *Inset.* High power detail of koilocytes showing enlarged cells with slightly irregular nuclei surrounded by a halo. HE × 250.

Results

Immunohistochemical examination of both the papillomatous lesion and typical ameloblastoma areas was negative. The in situ hybridization technique revealed HPV DNA type 18 in the papillomatous lesion (Fig. 3). The blocks containing the typical ameloblastoma features, including foci of granular cell and acanthomatous differentiation, were negative for the HPV DNA types examined.

Discussion

Radiolabelled HPV DNA in situ hybridization was used instead of the more commonly used biotinylated DNA in situ hybridization because it is a more sensitive method to detect HPV DNA (11). The sensitivity of the radiolabelled HPV DNA probe is 20–100 genome copies per cell compared to the 100–800 genome copies per cell of the biotin-labelled HPV DNA probe (1). The negative immunohistochemical staining in our study may be due to the fact that this technique identifies only the productive phase of the viral infection. Furthermore, as this method is based on an antigen-antibody reaction, the target antigenic determinants may be distorted by heating in paraffin, fixation in formalin or digestion by trypsin (12).

The presence of HPV type 18 DNA in a primary intrabony tumor of odontogenic epithelial origin is difficult to explain. Contact between the tumor epithelium and the oral mucosa may have facilitated cross-infection between oral epithelium and the ameloblastoma. Although no ulceration of the oral mucosa or skin was noted in this patient, expansion of the buccal and lingual cortices with erosion of the buccal cortex in the right premolar area were present. This area corresponded with the location of the papillomatous lesion in the ameloblastoma. The specimen was thoroughly examined for the presence of similar lesions without success, supporting the link between the HPV-associated lesion and the eroded bone cortex. Direct contact between tumor epithelium and surface epithelium could not be demonstrated.

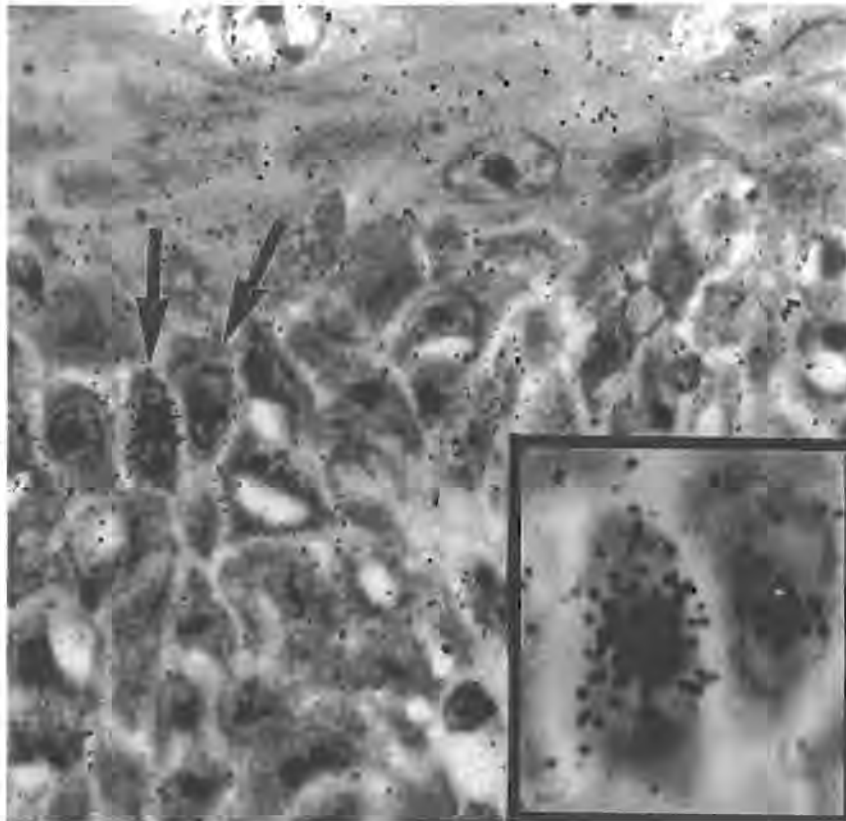Cox *et al.* demonstrated HPV 16 DNA in an odontogenic keratocyst

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Fig. 3. Micrograph of the verrucous lesion subjected to in situ hybridization shows the presence of HPV 18 DNA as condensations of black silver grains superimposed on the nuclei (arrows). × 200. *Inset.* High power detail of positive cells. × 400.

lacking the typical histologic features of an HPV infection (8). This HPV was implicated in the pathogenesis of the odontogenic keratocyst because the keratin-producing lining of the cyst provided squamous epithelium for viral persistence as well as completion of the virus life cycle. HPV 18 has an even higher oncogenic potential than HPV 16 (13), and has also been detected in oral epithelial dysplasias and oral squamous cell carcinomas (14). In our case HPV DNA was detected only in the solitary papillomatous lesion and not in the other epithelial regions permissive for viral infections, i.e. the acanthomatous and granular cell areas. We feel that the restriction of HPV DNA positivity to the verrucous lesion represents a secondary infection and is therefore not an etiological factor in the pathogenesis of this ameloblastoma.

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Infrequent clinicopathological findings in 108 ameloblastomas

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Raubenheimer EJ, van Heerden WFP, Noffke CEE: Infrequent clinicopathological findings in 108 ameloblastomas. J Oral Pathol Med 1995; 24: 227–32. © Munksgaard, 1995.

One hundred and eight ameloblastomas diagnosed in a rural black Africa population were analysed for clinicopathologic findings other than those classically described. One patient had a polycystic ameloblastoma adjacent to an ameloblastic fibroma. Two other polycystic ameloblastomas showed aneurysmal bone cyst formation and one mandibular tumour was diagnosed as a keratoameloblastoma. Microscopic changes resembling an adenomatoid odontogenic tumour were present in association with two unicystic ameloblastomas and a HPV18-positive verrucous lesion occurred in the lining of a cystic space of a polycystic ameloblastoma. Two ameloblastomas contained eosinophilic granules in all tumor cells and melanocytes were diffusely present in another. One case exhibited a focus of mucous cell metaplasia. Two polycystic ameloblastomas showed diffuse interstitial ossification. One mandibular tumor was diagnosed as a desmoplastic ameloblastoma and another as an odontoameloblastoma. This study demonstrated that although ameloblastomas are regarded as a fairly homogeneous group of neoplasms, detailed investigations prove clinicopathologic diversity in a significant number of lesions.

Ameloblastoma is the most common neoplasm affecting the jaws. It is derived from odontogenic epithelium and although located primarily intraosseously, peripherally occuring ameloblastomas involving soft tissue only have occasionally been reported. Two clinicopathologic variants of intraosseous ameloblastomas are commonly recognised. Polycystic ameloblastomas occur mainly in the body and ascending ramus of the mandible and most patients with this type present in the 4th decade of life (1). Unicystic ameloblastomas present on average a decade earlier (2) and are generally associated with a lower post-operative recurrence rate then the polycystic types. They can be divided microscopically into Groups 1, 2 or 3 depending on either the presence of a non-proliferating lining, intraluminal proliferations or mural invasion respectively (2). Ameloblastomas may occur more frequently in black Africans than in other racial groups (3).

Several recently published large series on ameloblastomas make no mention of coincidental and infrequent clinicopathologic findings (2–5) and most information about these is obtained through individual case reports. The secretion of interleukin-1 and a parathyroid hormone-like substance by an ameloblastoma was alleged to be the cause of hypercalcemia in one patient (6). A multilocular lytic mandibular lesion in a patient with hyperparathyroidism was proven microscopically to represent an ameloblastoma associated with a brown tumor of hyperparathyroidism (7). The occurrence of an ameloblastoma in a patient with the basal cell nevus syndrome (8) appears to be a sporadic rather than a regular feature. Other tumors that have been reported to be associated with ameloblastomas include the calcifying odontogenic cyst (9), acinic cell carcinoma and adenolymphoma of salivary gland origin (10), osteogenic sarcoma (11), traumatic neuroma (12) and aneu-

rysmal bone cyst (13). HPV capsid antigen was proven positive with the immunoperoxidase staining technique in 3 out of 10 ameloblastomas in children (14) and mucormycosis infection was reported to have been superimposed on an ameloblastoma in an elderly diabetic woman (15). Stromal desmoplasia in a significant number of ameloblastomas has led to the use of the term 'desmoplastic ameloblastoma' (16) and extensive interstitial bone formation in ameloblastomas has recently been reported in two Japanese patients (17, 18). A case of papilliferous keratoameloblastoma was reported by ALTINI et al. (19) and other microscopic rarities include melanocytes between (20), and granular cell change in all tumor cells (21).

The purpose of this study was to determine the spectrum of uncommon clinical and pathological findings in a large sample of ameloblastomas diagnosed in a rural black African population.

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Material and methods

Clinical records, radiographs and hematoxylin and eosin-stained microscopic slides of biopsies and surgical resections of 108 primary intraosseous ameloblastomas were scrutinized for extraordinary and coincidental pathologic features. At least four wax blocks were available in most cases. The following special staining techniques were employed on selected cases: Mucicarmine for epithelial mucins, Masson-Fontana for melanin, Perl's Prussian blue for hemosiderin pigment and the *in situ* hybridization technique for the presence of HPV antigen. All cases were diagnosed and treated in the Medunsa Dental Hospital which serves a black and mainly rural African community.

Results

The sample consisted of 108 ameloblastomas of which 75 were polycystic and 33 unicystic. All cases originated intraosseously. The sex and age distributions are shown in Table 1. All polycystic and 29 of the unicystic ameloblastomas occurred in the mandible and four unicystic ameloblastomas presented as maxillary swellings. The left mandible was involved in 65 cases, right mandible in 26 and symphysis area in 13 cases. Twelve polycystic and 4 unicystic ameloblastomas perforated the bony cortex and caused soft tissue ulceration. A mandibular ameloblastic fibroma in a 19-year-old woman was adjacent to and continuous with a polycystic ameloblastoma (Fig. 1). Aneurysmal bone cyst changes were identified in the latter patient as well as in another polycystic ameloblastoma in a 20-year-old woman. A polycystic ameloblastoma which involved the anterior mandible of a 13-year-old girl was associated with a compound odontome (Fig. 2).

Microscopically, 47 polycystic ameloblastomas were follicular, 23 plexiform and 5 were of mixed follicular and

Fig. 1. A resected specimen showing a polycystic ameloblastoma associated with an ameloblastic fibroma (arrows).

Fig. 2. Panoramic radiograph of the odontoameloblastoma.

plexiform patterns. The stellate reticulum showed no differentiation in 35 cases, 22 cases presented with acanthomatous differentiation, 9 cases with granular cell differentiation, 6 cases with both granular cell and acanthomatous differentiation, and basal cell differentiation was seen in one case. A follicular ameloblastoma showed acanthomatous differentiation and foci of mucous cell metaplasia (Fig. 3). One tumor, which occurred in the mandible of a 57-year-old woman, showed extensive keratinisation and was diagnosed as a keratoameloblastoma. The unicystic ameloblastomas showed mural invasion in 15 cases and intraluminal proliferation in one case. The remaining 17 unicystic ameloblastomas were lined by

non-infiltrative epithelium. In 9 of the latter group, less than 3 blocks were available for microscopic examination. Microscopic changes resembling an adenomatoid odontogenic tumor were presention the walls of two unicystic ameloblastomas (Fig. 4). HPV type 18 was identified in a verrucous lesion which occurred in a polycystic ameloblastoma and in one case melanocytes were uniformly present between the neoplastic epithelial cells. In two patients aged 15 and 26 years respectively, ameloblastic epithelium contained eosinophilic granules in all tumor cells (Fig. 5). Hemosiderin pigment was identified in the cytoplasm of neoplastic odontogenic epithelial cells next to an area of hemorrhage. A desmoplastic re-

Table 1. Sex and age distribution

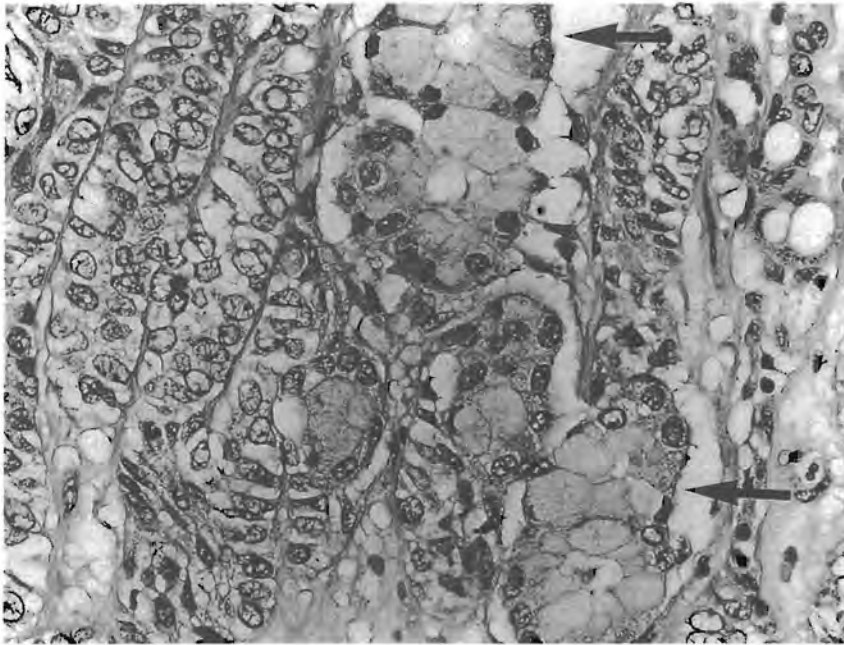|		Sex		Average age (range in years)
	N	M	F	
Total sample	108	50	58	29.3 (8–84)
Polycystic	75	33	42	35.4 (13–84)
Unicystic	33	17	16	16.5 (8–37)

Fig. 3. Mucous-cell metaplasia (arrows) in an ameloblastoma (H&E, X240).

action was a common feature in the extraosseous component of ameloblastomas which perforated the bony cortex. Desmoplasia of the intrabony part of ameloblastomas was variable both between tumors and within the same tumor and depended upon the degree of inflammation. Only one case was diagnosed as a desmoplastic ameloblastoma on the basis of a uniform and mature connective tissue proliferation in the absence of inflammation and which impinged upon the neoplastic epithelial component (Fig. 6). Two polycystic ameloblastomas were associated with diffuse interstitial bony deposits which led to radiographic diagnoses of fibroosseous lesions.

Discussion

Large series published on ameloblastomas often make no mention of features other than those classically described and most infrequent findings are re-
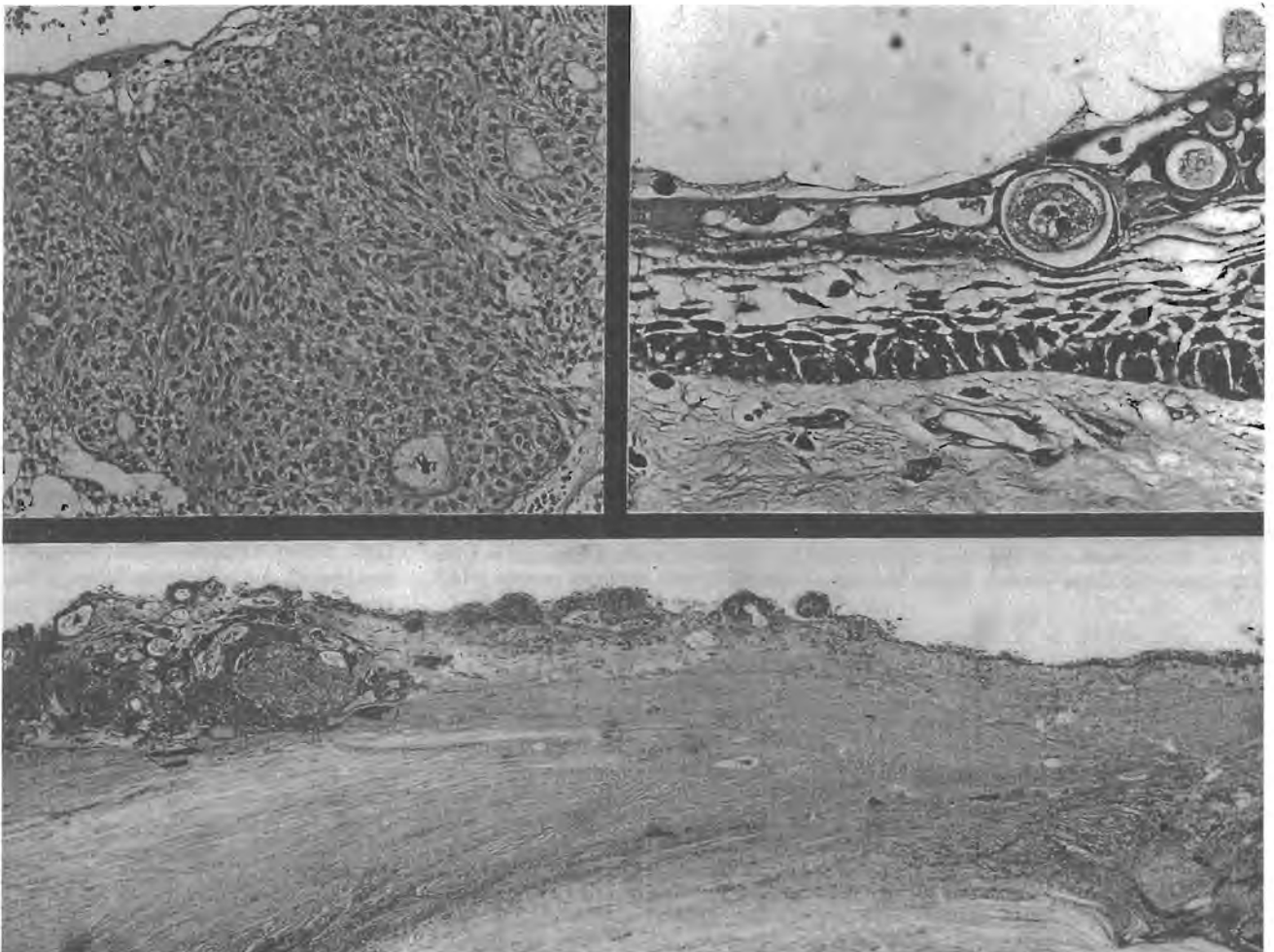

Fig. 4. A unicystic ameloblastoma (right side of low power view and top right insert) which exhibited adenomatoid odontogenic tumour differentiation (left side low power view and top left insert). (H&E, ×40, X120, X200).
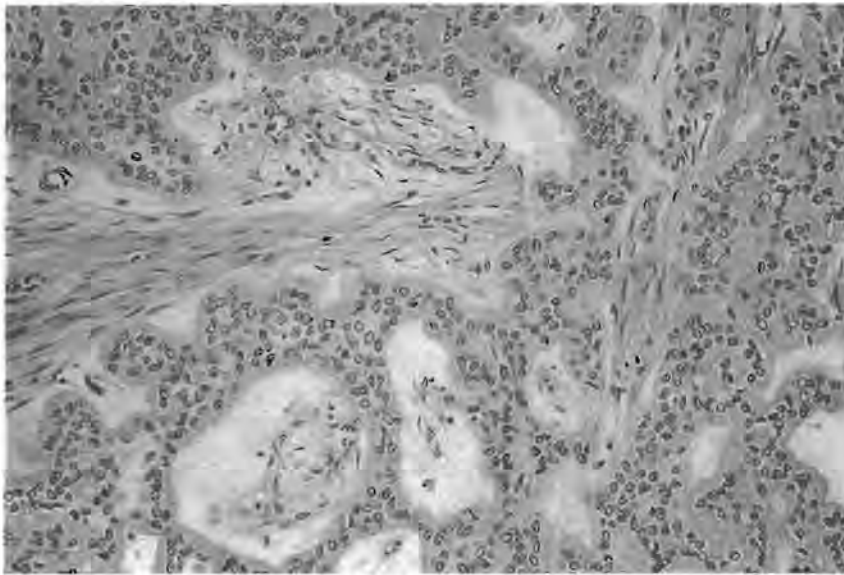
Fig. 5. A plexiform proliferation of ameloblastic epithelium exhibiting granules in all tumour cells. Typical features of ameloblastoma were not present (H&E, ×180).
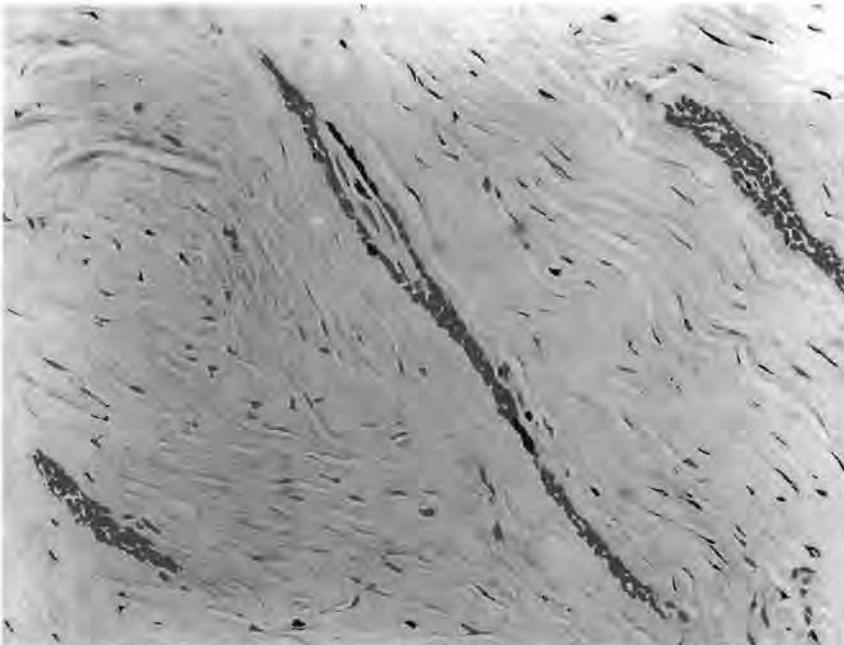

Fig. 6. Desmoplastic ameloblastoma characterized by compressed epithelial strands in a mature connective tissue stroma. Typical features of ameloblastoma were not present (H&E, ×180).

ported as case studies. This has led to a generally accepted view that ameloblastomas are fairly homogeneous in their clinical and pathologic presentation. This review was undertaken to establish the spectrum of extraordinary and coincidental clinical and pathologic findings in a large collection of ameloblastomas diagnosed in a rural African population.

In the total sample, the left mandible was affected 2.5 times more commonly than the right. Although there appears to be no apparent explanation for left mandibular predominance in our study, this finding is supported by a large Japanese series in which only 40% occurred on the right hand side (4).

The subclassification of unicystic ameloblastomas according to the microscopic appearance of the lining (2) was found to be impractical. Although areas of intraluminal proliferation or mural invasion positively confirmed un-

icystic ameloblastomas in Groups 2 and 3 respectively, the subdivision into Group 1 lesions was found to be of limited value unless the whole tumor was processed for microscopic examination. In the case of large unicystic ameloblastomas, this was either impractical or even impossible, making the microscopic identification of foci of mural invasion in larger lesions unlikely. This dilemma is clearly illustrated in our study where fewer than three wax blocks were available for microscopic examination in 9 cases ultimately subclassified as Group 1 unicystic ameloblastomas.

Tumors which occur within bone generally predispose to pathologic fracture and aneurysmal bone cyst formation (22). Both these findings are, however, infrequently reported in association with ameloblastomas. The presenting symptom in only three of our patients was directly associated with pathologic fracture of the mandible. Aneurysmal bone cysts are reported to be rare in the jaws, occur mainly in young patients, and approximately one-third are found in association with other pathologies (23). A microscopic study of 42 ameloblastomas found hallmarks of aneurysmal bone cysts in 7 (13). Although the frequencey of aneurysmal bone cyst change in our study was not as high, both our cases occurred in young patients. The coexistence of aneurysmal bone cyst with ameloblastoma is significant because of the excessive bleeding which may be encoutered during surgery.

The association of an ameloblastic fibroma with ameloblastoma has not previously been reported. The example described here could be regarded as coincidental, as the patient was at an age when ameloblastic fibroma occurs most frequently. Simultaneous occurrence of ameloblastoma and odontoma is rare (24). These tumors, which have been designated as odontoameloblastomas, consists of epithelial proliferations typical of ameloblastomas associated with highly differentiated dental tissues either scattered throughout the tumor or, as in our case, as a single radiopaque mass (1). Squamous metaplasia is a well described and variable feature in ameloblastoma. Extensive squamous change, where follicles consist entirely of squamous epithelium with only traits of the original ameloblastomatous structure, is less frequent (23). One tumor in our series, which occurred in an elderly woman patient, exhibited this change and was diagnosed as a kera-

toameloblastoma. Although adenomatoid odontogenic tumor-like differentiation has been reported in a dentigerous cyst (25), this change in a unicystic ameloblastoma has not yet been described. Both our examples occurred in the anterior mandible and this, together with the hitherto undescribed phenomenon of mucous cell metaplasia, illustrates the differentiation potential of ameloblastic epithelium.

The presence of an HPV-induced verucca in the epithelial lining of a polycystic ameloblastoma adds an interesting parameter to the study of papillomavirus-induced epithelial proliferations. These lesions occur commonly on the skin and lining mucosa, to our knowledge this case, which was published recently (26), represents the first description of a verucca in a cystic epithelial tumor, the lining of which was within bone and not in contact with the oral mucosa. The origin of the melanocytes in odontogenic tumors and cysts is speculative. The cells of the neural crest interact in the development of teeth and it is not surprising that melanocytes can occur in odontogenic tissues. Although it is believed that melanotic odontogenic tumors occur more frequently in black patients (25), the number of cases reported is too low to draw conclusions. Our one melanotic ameloblastoma in the 108 cases studied places the frequency of this phenomenon below 1% in a black African sample and thus can hardly be regarded as common. The presence of hemosiderin in the neoplastic epithelium adjacent to an area of hemorrhage emphasizes the phagocytic capacity of neoplastic odontogenic epithelium. Varying amounts of granular cells are seen in the stellate reticulum of granular cell ameloblastomas. However, the presence of granules in all cells, including the peripheral layer, is rare. We believe this feature, which was present in two of our cases, represents full expression of granular cell differentiation. The plexiform granular cell odontogenic tumor reported by ALTINI *et al.* (1986) (27) is probably an example of this variant.

Quantification of stromal desmoplasia was found to be difficult as it varied between tumors and within the same tumor. Generally, ameloblastomas which infiltrate soft tissue and those which are inflamed exhibit more desmoplasia than others. Terminology such as "desmoplastic ameloblastoma' (16) should be used with great circumspection as

the intensity of the desmoplasia is variable and forms part of a continuous spectrum of stromal fibroplastic reaction in ameloblastomas. We suggest that certain criteria must be applied before the diagnosis of a desmoplastic ameloblastoma is made. These should include the absence of inflammatory changes and cortical bone perforation as well as the uniform presence of a mature, diffuse collagenous stromal tissue compressing the neoplastic epithelial component into strands. The two tumors which contained extensive interstitial bony deposits resemble the Japanese cases published recently (17, 18) and their clinical and radiographic differentiation from benign fibro-osseous proliferations is a pitfall to be avoided. The prominent bone formation appeared to be reactive in nature, probably linked to a process of interstitial connective tissue metaplasia rather than a result of induction, as the bony deposits were generally separated from the neoplastic epithelium by a broad band of inactive connective tissue. Unlike a recently published paper (28), we believe the desmoplastic and osteoplastic ameloblastomas are not distinct clinicopathologic entities but rather variants of the microscopic spectrum of stromal reactions in ameloblastomas.

This study demonstrates that although ameloblastomas are generally regarded as a homogeneous group of neoplasms, detailed investigations prove clinicopathologic diversity in a significant number of tumors. Many of these changes emphasize the differentiation potential of neoplastic odontogenic epithelium and add interesting parameters to the study of tissue reactions associated with this common odontogenic tumor.

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ORAL SURGERY,
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Calcifying epithelial odontogenic tumor with intracranial extension: Report of a case and review of the literature

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The calcifying epithelial odontogenic tumor (CEOT) is a rare benign neoplasm, possibly of stratum intermedium origin and occurring predominantly in the mandible of adults. The treatment varies, depending on its size, location, and histology. A case of an advanced CEOT arising in the maxilla with intracranial extension is reported. The report is supplemented by a review of the literature. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000;90:656-62)

The calcifying epithelial odontogenic tumor (CEOT) is a rare benign odontogenic neoplasm of the jaws. Many names have been given to this lesion.[1] Pindborg[2] was the first to describe this lesion as a separate clinicopathologic entity, and he named it a calcifying epithelial odontogenic tumor. Today, nearly 200 cases have been reported in the literature. The origin of this neoplasm is controversial, though it is generally accepted to have derived from the oral epithelium, reduced enamel epithelium, or stratum intermedium.[3-7] Pindborg's proposed origin, from reduced enamel epithelium, is plausible because more than half are associated with unerupted or impacted teeth.[2] Chaudry's histochemical studies support the theory that the CEOT arises from the stratum intermedium.[4,8]

Clinically, CEOT manifests as an intraosseous lesion (central type) in the majority of cases (95%). Extraosseous or peripheral lesions account for less than 5% of cases. The latter are usually in the anterior region of the jaws. Most investigators agree that the central type is usually located in the premolar and molar regions, with a mandibular to maxillary ratio of 2 to 1. The majority of CEOTs (52%) are associated with impacted or unerupted teeth.[1,2] There is an almost equal distribution

between men and women. The age of the patients affected by this tumor ranges from 8 to 92 years, with a mean age of 40. This neoplasm occurs in different population groups, with a slight predilection for whites.[1,2] However, this may merely reflect a reporting bias. The most common radiographic finding is a well-defined unilocular radiolucency, which resembles a dentigerous cyst. The neoplasm may appear as a multilocular lesion mimicking an ameloblastoma. Classically, areas of scattered flecks of calcifications in the central radiolucency may be seen; however, calcifications may sometimes not be evident on radiographs.[1]

The histologic criteria listed by Franklin and Pindborg[1] and others[6,8-11] for the diagnosis of CEOT are sheets of polyhedral epithelial cells that have well-defined borders and often show prominent intercellular bridges. There is usually pleomorphism of the epithelial cells, and the nuclei and nucleoli are often prominent. Mitotic figures are rarely seen. A characteristic feature within the sheets of epithelial cells is circular areas filled with a homogeneous substance resembling amyloid-like material, which stains positively with Congo red. Some of these cells are also filled by calcified material in the form of concentric Liesegang's rings, which are pathognomonic of this tumor.[3,8-10,12]

Recently, variants of CEOT, which may have a bearing on the prognosis and management, have been described. Three such variants reported in the English literature are the noncalcifying CEOT with Langerhans' cells, the CEOT displaying cementum-like and bone-like material, and the clear-cell CEOT.[12-17] The former variant of noncalcifying epithelial odontogenic tumor is histologically similar to the peripheral type of

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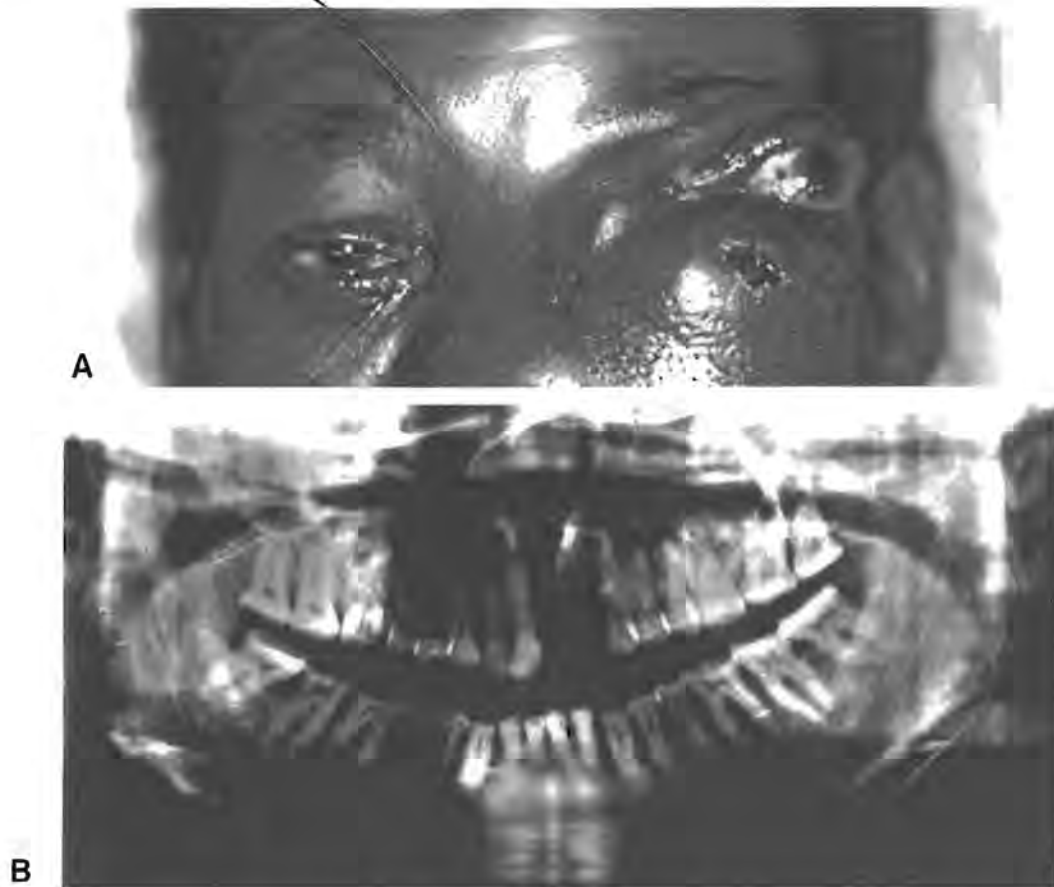[b]Department of Oral Pathology, Medical University of Southern Africa, Republic of South Africa.

Fig I. **A.** Large swelling of left face causing severe left orbital dystopia. Note fistula below left eye. **B**, Panoramic view of patient showing large, poorly demarcated lytic lesion with missing left central and lateral incisors.

CEOT but is devoid of calcifications, and one may speculate that this variant's clinical behavior would be less aggressive than the peripheral lesion.[12,13] It has been proposed that CEOTs with more amyloid and calcifications could be treated less aggressively.[8,18] CEOTs with large amounts of bone-like or cementum-like material probably indicate a higher level of differentiation and thus may account for their more self-limiting behavior, unlike the ameloblastoma.[19] The clear-cell CEOT variant is more aggressive with a higher recurrence rate (22%), and some would consider this form to be a low-grade odontogenic carcinoma.[20]

In 1984, Basu et al[3] reported a malignant CEOT that showed evidence of local tissue invasion and regional lymph node metastasis.[8,20] There have also been reports of various other odontogenic lesions occurring in association or in combination with CEOT. These include dentigerous cysts[5] and adenomatoid odontogenic tumors,[6,13] as well as presentation of CEOT as an intramural lesion of the dental sac.[7,8]

The purpose of this article is to report an unusual CEOT arising in the maxilla that has expanded into the

cranial cavity, causing orbital dystopia and severe intracranial complications.

CASE REPORT

A 54-year-old black man was referred to the Department of Maxillofacial and Oral Surgery by a rural clinic for assessment of a large swelling, causing severe left orbital dystopia and gross facial asymmetry (Fig I, *A*). His family had noticed that he struggled to maintain his balance, and he presented with urinary incontinence. He had noticed this slow-growing lesion for a number of years, but had neglected to report it to his clinic because it was asymptomatic. His medical history was completely unremarkable, with no evidence of systemic diseases. The patient had no vision in his left eye. Below this eye was evidence of a pus-draining fistula. No regional nerve paresthesia or lymphadenopathy was present. Intraorally, there was a firm, expansile lesion, involving the left maxilla, with obliteration of the left maxillary buccal vestibule. There was no palatal expansion. The oral mucosa was intact and normal in color. The left maxillary central and lateral incisors were extracted many years ago. The patient had very poor oral hygiene. A panoramic radiograph showed a large, poorly demarcated lytic lesion with irregular areas of opacities involving the left maxillary sinus and orbit (Fig I, *B*). The differential diagnosis included cemento-
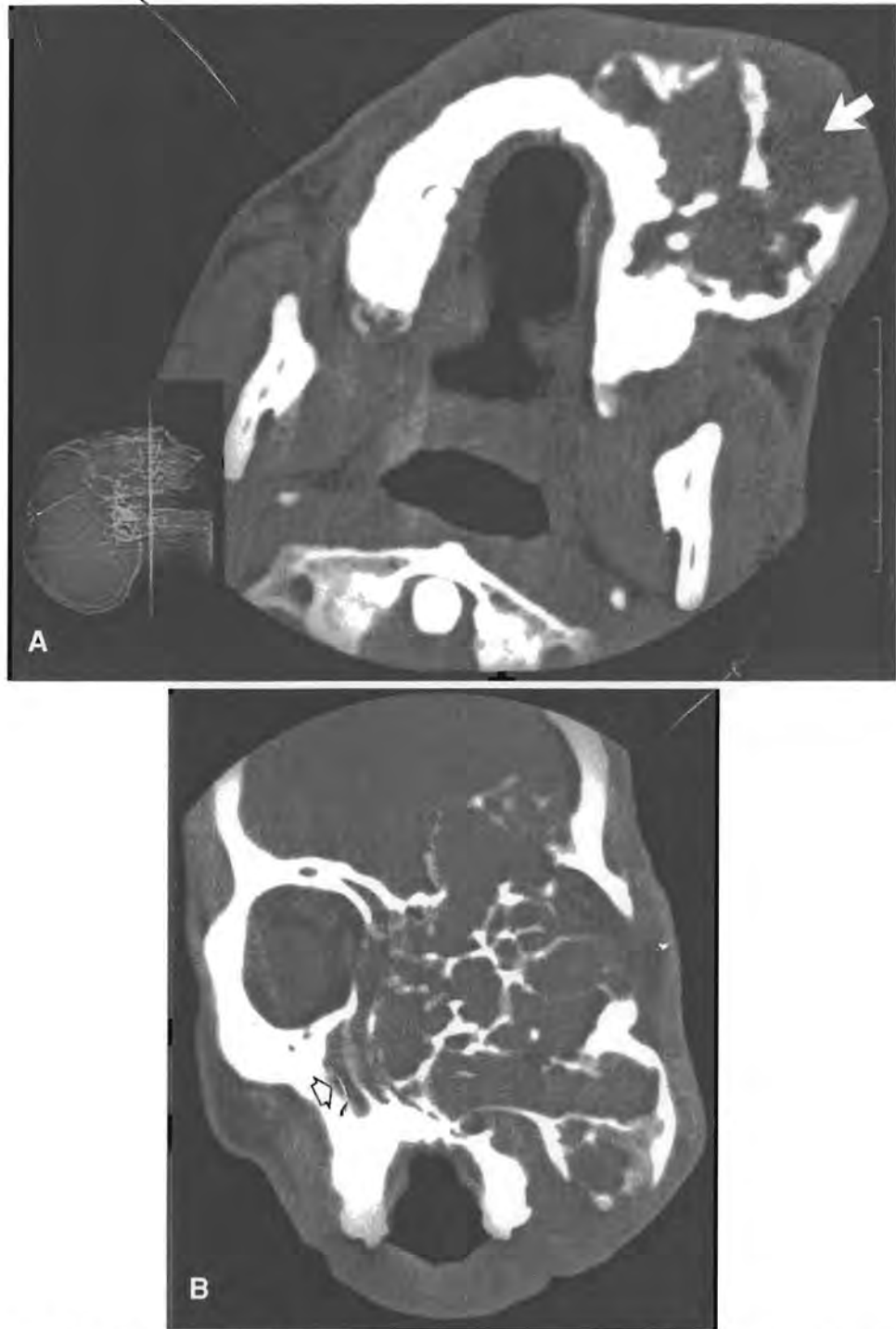
Fig 2. **A**, Axial CT scan at level of maxilla showing buccal expansion and cortical perforation *(arrow)*. **B**. Coronal CT scan through orbits showing tumor expanding intracranially, obliterating left maxillary antrum. left orbit, nasal cavities, ethmoidal sinus, left frontal sinus, and displacing medial wall of right antrum *(arrow)* and of right orbit. Note lack of palatal expansion.

ossifying fibroma, ameloblastic odontoma, and CEOT. Computed tomography (CT) scans of the maxilla and orbits were obtained to show axial and coronal sections of the soft tissues and facial bones. A well-circumscribed isodense mass with expanding radiopaque margins containing areas of irreg stellate opacities was seen (Fig 2. *A* and *B*).

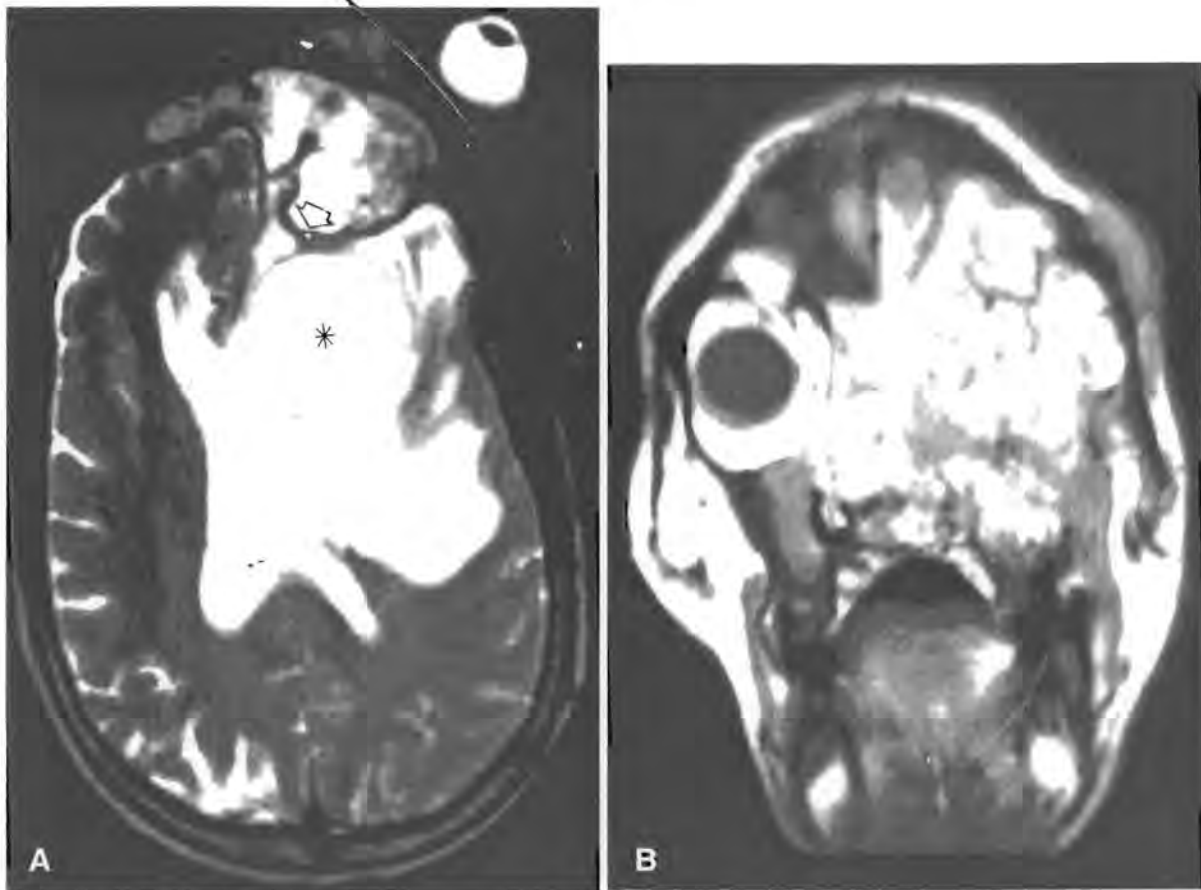Magnetic resonance imaging showed a massive tur destroying the left maxilla through to the anterior cra

Fig 3. **A.** Axial magnetic resonance scan (T² series) showing displaced left eye and tumor extending into frontal area *(arrow)*. Note well-circumscribed mass *(asterisk)* posterior to tumor. **B,** Coronal magnetic resonance scan (T₁ series) showing massive infiltration into frontal area of brain.

fossa. The tumor invaded the left orbit and displaced the left eye anterosuperolaterally (Fig 3, A). The left eye showed no infiltration by tumor.

There was invasion of the right orbit and the right antrum. The tumor infiltrated through the ethmoid sinuses and the cribiform plate into the frontal area (Fig 3, B). There was also a large, well-circumscribed fluid-retained area in the frontal lobe, which may have been an abscess with surrounding brain edema. The midline of the brain was displaced to the right with compression of the adjacent right ventricle (Fig 4).

An angiogram of the left internal and external carotid artery was done with the Seldinger technique. The intracranial extension of the tumor showed displacement of the middle cerebral artery laterally and the anterior cerebral artery medially (Fig 5). An incisional biopsy of the left maxillary vestibule was performed with the patient under local anesthesia. The patient was admitted to the academic hospital for further preoperative workup. Histologic examination showed a fibrous connective tissue capsule surrounding sheets of pleomorphic polyhedral epithelial cells, containing nuclei of varying forms and sizes and lacking mitotic activity. An extracellular eosinophilic material resembling amyloid was focally present. There were concentric calcifications with

Liesegang rings (Fig 6). The histologic diagnosis was CEOT.

The Department of Neurosurgery was consulted, and the patient was prescribed methylprednisolone to alleviate brain edema. He showed dramatic recovery of neurologic symptoms and requested to be discharged. At his follow-up visit a month later, the patient had noticed a large amount of pus draining from below the left eye. His condition further improved over the next few days. A CT scan showed a significant reduction in the size of the fluid-filled space in the frontal area of the brain. Several treatment options were explained to the patient and his family. The patient requested a temporary discharge and was then lost to follow up.

DISCUSSION

CEOT is a rare benign epithelial odontogenic neoplasm that was first described by Pindborg in an abstract in 1955 and again as an article in 1958.[1,2] Though this tumor is benign, a few cases have been reported as locally aggressive, invading surrounding
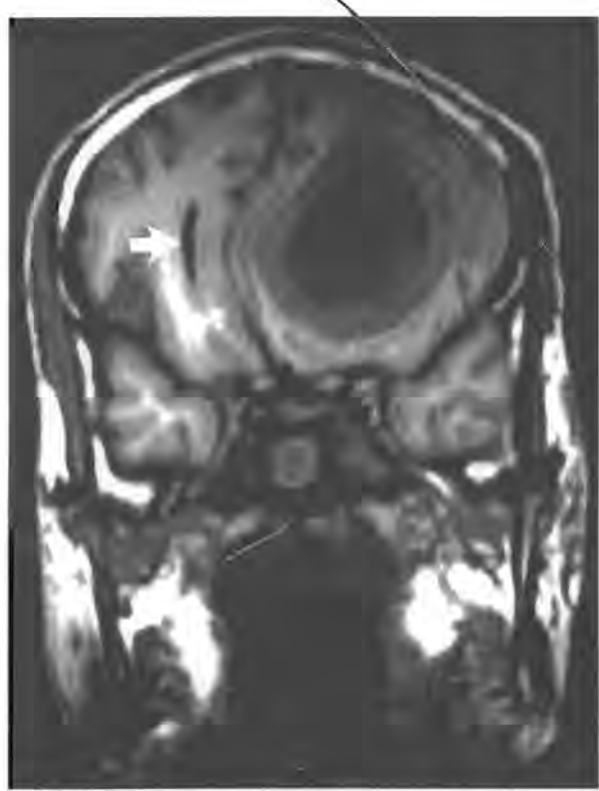
Fig 4. Magnetic resonance imaging (coronal view) showing large, well-circumscribed area causing midline shift, obliteration of left ventricle, and compression of right ventricle *(arrow)*.
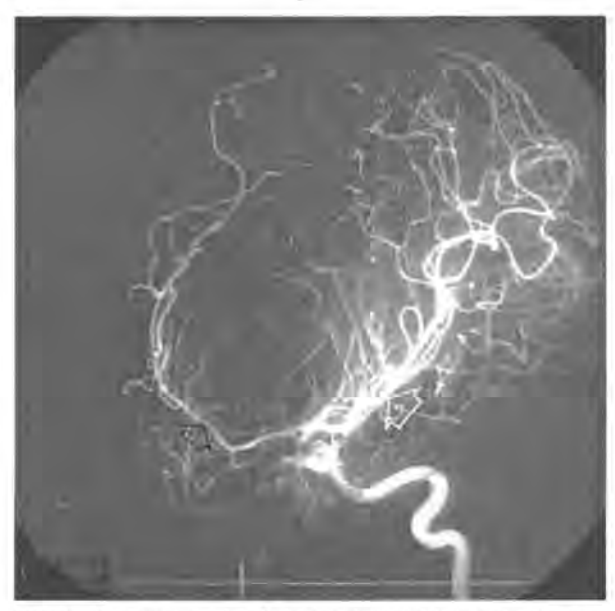

Fig 5. Angiogram of left internal carotid artery, showing lateral displacement of middle cerebral artery *(white arrow)* and medial displacement of anterior cerebral artery *(black arrow)*.

soft tissues and bone.[21] CEOTs account for less than 1% of all odontogenic tumors.[1,2]

Ficarra et al[7] suggested that the neoplasm arises from cell remnants frequently seen in the wall of the dental sac that resemble the reduced enamel epithelium. Regarding the extraosseous-type lesions, the origin is less certain,[8] but Ai Ru et al[22] suggested that the peripheral type arises from oral epithelium. The prevalence in the molar region is 3 times that of the premolar area. Fifty-two percent of cases are associated with an unerupted tooth.[1] It would appear that our case also arose from the anterior maxilla or from the wall of the maxillary sinus and then expanded over the years by the path of least resistance through the maxillary sinus to the ethmoid sinus, eroding the cribiform plates into the frontal area. No palatal expansion was evident, despite extensive orbital and intracranial involvement. CEOT arising in the maxillary sinus is extremely rare.[23] Three other cases have been described in the English literature of CEOT that possibly originated in the maxillary sinus wall.[21,24,25]

The clinical features are usually those of a painless, slow-growing intraosseous mass. However, a tumor in the maxilla may cause pain, nasal obstruction, epis-

taxis, headaches, and proptosis.[1,19] Our patient gave no history of any of the above symptoms, and only when neurologic symptoms occurred did he seek help. Although intracranial extension was demonstrated beyond doubt, the large fluid-filled space in the frontoparietal area of the brain was probably not part of the tumor. The pus that drained from below the left eye was followed by a reduction in size of the fluid-filled space, making it likely to be a brain abscess. It is proposed that distortion of the paranasal sinuses may have resulted in blockage of drainage and sinus infection, which extended into the brain.

Treatment options for CEOT have ranged from simple enucleation to radical and extensive resection.[8] Several authors initially advocated aggressive treatment, but increasingly, histologic information shows that this tumor does not appear to extend into the intertrabecular bony spaces as does an ameloblastoma[1,19]; therefore, a more conservative approach is warranted.[10] Sadeghi and Hopper[26] believe the surgical treatment of CEOT should be guided by the site, size, and the histologic features of the lesion. Thus, maxillary neoplasms would be treated more aggressively because of their close proximity to vital and important structures,[23] whereas mandibular lesions could be approached more conservatively. Our intended treatment plan was primarily to debulk the tumor and then later, with reconstructive procedures, to repair soft and hard tissue defects. A modified Weber incision, which would continue superi-
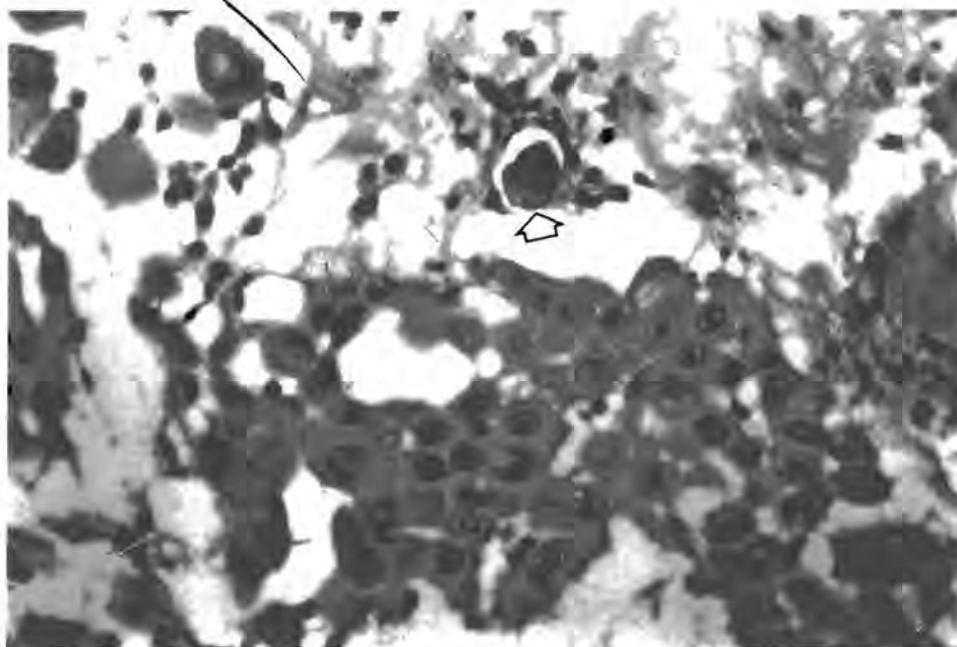
Fig 6. Polyhedral epithelial cells with concentric calcification *(arrow)* (hematoxylin-eosin, original magnification ×200).

orly as a paranasal incision that extends onto the forehead vertically to join the superior limb of a left temporal flap, would have allowed the whole facial skin to reflect laterally, giving direct access to the maxilla, cribriform plate, and ethmoid area. The patient unfortunately declined surgery and was lost to follow-up.

Our case demonstrates that, although CEOTs are benign, neglect of a maxillary lesion can lead to serious intracranial involvement, which could severely complicate patient management.

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Hodgkin's disease presenting in the maxilla

A case report

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Abstract. A rare case of intra-oral, extra nodal, maxillary Hodgkin's disease
(Stage I), with no other discernible tissue involvement is described and discussed.
The pertinent literature is reviewed.

Hodgkin's disease, a malignant lymphoma first described by Thomas Hodgkin in 1832[12], occurs most commonly in the 20- to 30-year age group, with a second peak in incidence after the age of 55 years. Males are said to be affected more frequently.

Presentation is most commonly in the form of a painless but progressive enlargement of lymph nodes in the neck. Extra nodal presentation with involvement of the spleen, bone marrow, skin, intestines and liver is less common. Malaise, fever, weight loss and pruritus are among the more frequently associated signs and symptoms.

Histologically, the disease is characterized by the presence of malignant lymphoid cells and inflammatory cells including lymphocytes, histiocytes, eosinophils and plasma cells; however Reed-Sternberg cells: large, multinucleated cells with very large 'owl-eye' neucleoli and 'mirror-image' nuclei, must be identified within this cellular background for the histological diagnosis to be made.

Classification of the disease is in accordance with the abundance of lymphocytes observed within the infiltrate. The Rye classification[15] is made following histological examination of an involved excised lymph node, and is based on the nature and pattern of lymphocytic infiltration of the node.

Prognostication of survival times must, however, take into account the staging of the disease, for which the Ann Arbor classification[5], based on the anatomical location of the lesion, is most widely followed.

Hodgkin's disease uncommonly involves bone clinically, and rarely involves the jawbone; primary involvement of the maxilla has only been reported once previously[20].

Case report

In January 1987, a 51-year-old black female attended her dentist complaining of mobile and painful 11 and 21 teeth. Both teeth were extracted.

Approximately 2 months later, the mucosa covering the crest of the alveolus at the extraction site ulcerated, with extension onto the palate and into the buccal sulcus. The ulcer was painful, and the patient reported a putrid taste. 2 months later, the patient consulted our unit.

On presentation, the patient's medical history revealed that despite a good appetite, she had recently lost weight. Clinically, the patient appeared anaemic; however a general physical examination failed to detect any other abnormalities. No lymphadenopathy was present.

Intra-orally, the mucosa overlying the alveolus between the 14 and the 23 had ulcerated with a similar area of palatal involvement (Fig. 1). The 14, 13, 12, 22 and 23 teeth were mobile, vital and protruded from the denuded, grey/black discoloured alveolar bone. The upper lip was oedematous and painful to the touch. A diagnosis of cancrum oris was made, with underlying anaemia, malnutrition and the trauma of tooth extraction being considered as precipitating causes.

Swabs for bacteriological investigation were taken from the area; haematological, electrolyte, serological, immunological and certain spesific tests were conducted; as chest radiographs and electrocardiographs were also taken, in order to exclude tuberculosis, syphilis and bilharzia amoungst other conditions. Abnormal findings included a haemoglobin level of 9 gm%, and a Klebsiella pneumoniae culture from the lesion.

Fig. 1. Necrosis and sloughing of the maxillary alveolar and sulcus mucosa with exposure of alveolar bone (arrow).

The patient was transfused 2 units of fresh, whole blood, placed on a high protein died, and administered appropriate antibiotics; debridement of the lesion with extraction of 12 was undertaken before covering the area with bismuth-iodoform paste and petroleum jelly gauze.

11 days following admission, the haemoglobin level was 14.5 gm%, and the exposed bone had been largely covered with granulation tissue, although swelling of the upper lip persisted. The patient reported night sweats. Pruritus was not present. Increased weight loss had not occurred.

Biopsy of the alveolus and lip in the region of 24 revealed a Hodgkin's lymphoma infiltrate consisting of Reed-Sternberg cells, mononuclear Hodgkin cells and a mixed inflammatory infiltrate (Fig. 2). Biopsies of a neck and groin lymphnode and bone marrow of the iliac crest and sternum revealed reactive changes only, with no evidence of lymphoma. Gastroscopy and gastric and duodenal biopsy were normal. Bone marrow needle biopsies of the iliac crest and sternum revealed hyperplastic changes only.

The patient was classified as having an extra nodal Stage I Hodgkins Lymphoma. Treatment with nitrogen mustard, vincristine, vinblastine, procarbazine, prednisone and oxhetazine, administered in a series of 8 cycles, was instituted. Following the first cycle of treatment, the response was dramatic, with complete clinical reversal of the lip and alveolar lesion occurring. The remaining cycles were administered. 1 year post-treatment, the patient has gained weight, reports an absence of clinical symptoms, and the oral lesion has healed (Fig. 3).
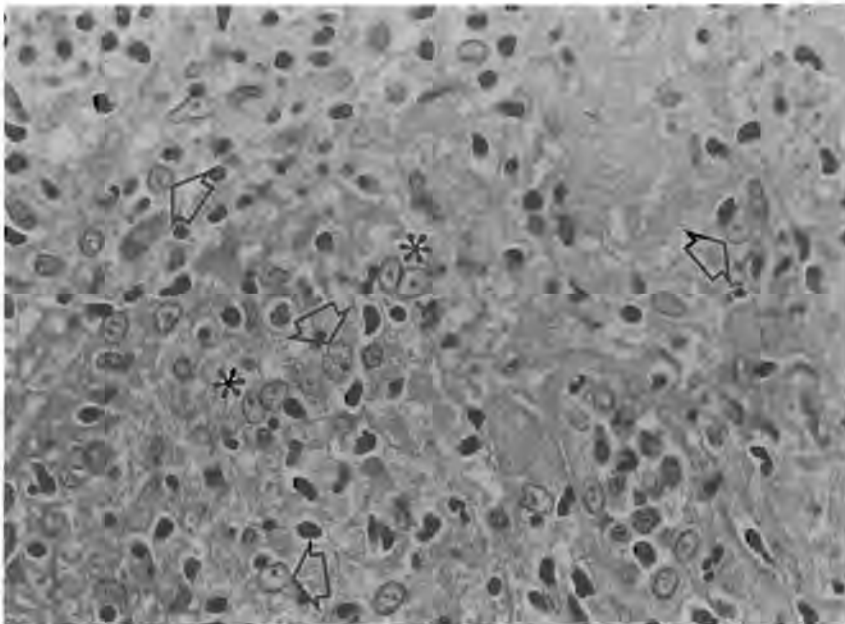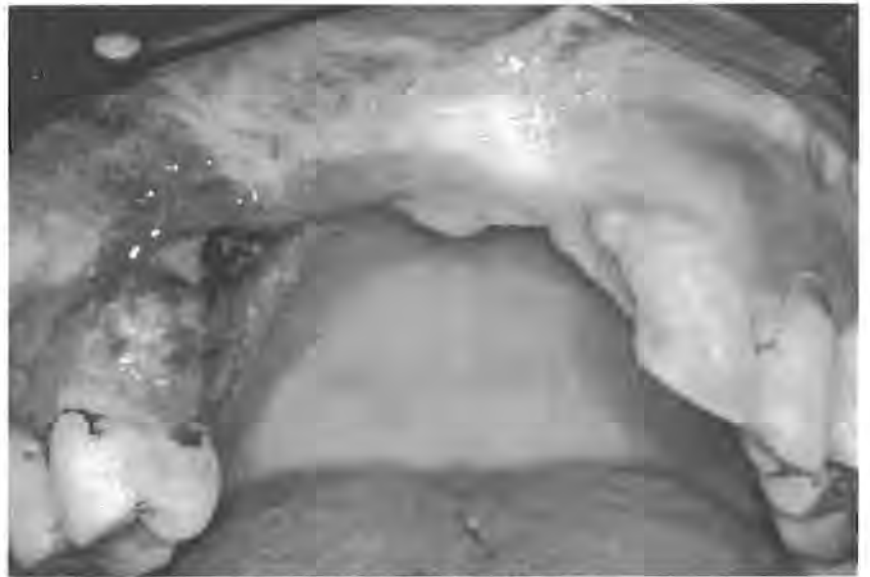

Fig. 3. 1-year post-operative, at the time of extraction of 13.

Discussion

The case described here is extremely unusual in that the patient presented with a Hodgkin's lymphoma lesion involving only extra nodal tissue. WOOD & COLTMAN[26] reported that Hodgkin's disease limited to the extra nodal sites had an incidence of 0.25%. Only 6 cases appear to have been reported to involve the oral mucosa[3,7,8,14,19,24].

Bone involvement in Hodgkin's disease was reported to have occured in only 269 of 2006 cases by STEINER[21], while JACKSON & PARKER[13] and GRANGER & WHITAKER[11] report the incidence of bone involvement to be 23% and 9.6%, respectively. BEARMAN et al.[4] report the range of bone involvement to be between 5% and 15%; however STEINER[21] cautions that bone biopsies at post-mortem are likely to reveal about a 78% bone involvement.

Hodgkin's lymphoma presenting as a primary bone lesion was said by MIRRA[17] to be in the region of 0.3% of all cases. Furthermore, of the 12 reported cases of Hodgkin's lymphoma affecting the jawbones[1,2,6,9,10,16,2–22,25], only 1 case has hitherto been reported as having presented as a primary lesion of the maxilla[20].

In our patient, the infected, cancrum oris-like lesion developing on the maxilla is in accordance with the findings of COHEN et al.[6], who suggest that the severe infection accompanying Hodgkin's lymphomatous involvement of the mandible in their reported case is probably a manifestation of the presumed T-cell dysfunction thought to underlie Hodgkin's disease[23].

Of interest is the comment of FORMAN & WESSON[9] that primary bone origin is unlikely, since no case existed on record at that time of Hodgkin's disease being confined to the skeleton alone. In the present case, clinical examination of the liver, spleen, skin, and histological examination of neck and groin lymph nodes, as well as of biopsies of gastric and duodenal mucosa, iliac crest and

Fig. 2. Mixed cellular infiltrate characteristic of Hodgkin's lymphoma. Note the Hodgkin's cells (arrows) and Reed-Sternberg cells (asterisks).

sternum, failed to detect Hodgkin's disease. Liver, spleen and mediastinal scanning or a staging laparotomy with biopsies of the liver, spleen and lymph nodes would be necessary to support or refute the likelihood of this case having only maxillary and oral mucosal involvement.

Although biopsy of the deeper portions of the alveolus as part of the debridement procedure histologically revealed the Hodgkin infiltrate to be widespread and deep within the alveolus, the possibility cannot be entirely ruled out that bone involvement was secondary to primary alveolar mucosal involvement.

Prognosis for stage I Hodgkin's disease would appear to be fair[15,18,23]. Bone involvement indicates a grave prognosis according to FORMAN & WESSON[9], with an overall survival rate when all cases of Hodgkin's disease are taken into account of 41%, dropping to 4% for those in whom bone lesions are detected clinically[11]. Despite this, our patient with Stage I extra nodal bone involvement, responded excellently to chemotherapy.

Prognosis following involvement of the jawbones has not been specifically reported; however 3 patients with Hodgkin's disease of the mandible[6,9,22] are reported to have died 15, 6 and 7 months following diagnosis, respectively.

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Low-grade intraosseous osteosarcoma of the jaws

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Two cases of low-grade intraosseous osteosarcomas are reported, bringing the total number of such osteosarcomas in the jawbones documented in recent literature to six. Our first case involved the maxilla of a 69-year-old man and the second involved the mandible of an 18-year-old girl. In clinical and microscopic appearance, these neoplasms resemble benign proliferations in many respects. Subtle differences include cortical bone destruction, soft tissue infiltration, irregular bone production with foci of abundant osteoid, and mild cellular atypia. Complete removal at the first attempt is of paramount importance, inasmuch as a significant percentage of these neoplasms recur as high-grade osteosarcomas if they are inadequately treated.
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Low-grade intraosseous osteosarcomas are rare, and they are often inappropriately diagnosed as benign neoplasms. They represented 1.9% of all osteosarcomas in the files of the Mayo Clinic[1] and 1% of osteosarcomas in a study conducted in Italy.[2] The lesion has an equal gender distribution and commonly affects a patient in the third decade of life.[3] Low-grade intraosseous osteosarcomas are of endosteal origin, and most occur in the metaphysis of the femur and tibia. In the Mayo Clinic series of 80 cases, 12 low-grade intraosseous osteosarcomas occurred in flat bones; 2 of these were in the mandible and 1 was in the maxilla.[3]

Microscopically, low-grade intraosseous osteosarcomas show an infiltrative growth pattern despite a low mitotic index and lack of significant cellular atypia. They are frequently misdiagnosed as fibrous dysplasia[4,5] or other benign fibro-osseous proliferations.[2,6]

The purpose of this study was to highlight the diagnosis of low-grade osteosarcoma and to emphasize its distinction from other benign proliferations of central bony origin.

CASE REPORTS

The files of the Department of Oral Pathology at Medunsa, which serves a mainly rural and periurban black African population, were searched for low-grade intraosseous osteosarcomas. Between 1985 and 1997, 36 cases of osteosarcoma were diagnosed. Of these, two were reported as low-grade intraosseous osteosarcomas.

Case 1

A 69-year-old man appeared for treatment with a complaint of a painless and rapidly enlarging swelling of the premaxilla of less than 4 months duration. On external examination, a tumor measuring 4 × 3 cm was seen to be elevating the upper lip (Fig. 1). The mucosal surface was ulcerated and the lesion was bony-hard. The maxillary incisors were absent. Radiographic examination showed both loss of the cortical plate and a bone-forming lesion, the posterior margin of which was well demarcated (Fig. 2). A clinical diagnosis of a benign osseous proliferation was made, and a biopsy was performed. Microscopic examination showed sheets and plates of mature bone with excessive osteoid formation focally. Mitotic activity was below 1 mitosis per 10 high-power fields. The lesion infiltrated through the labial cortical plate of the maxilla around groups of submucosal minor salivary glands (Fig. 3) and extended into the base of the ulcer on the labial mucosa. A diagnosis of a low-grade intraosseous osteosarcoma was made, and the tumor was removed with wide excision.

Case 2

The second case involved the right mandible of an 18-year-old girl. She appeared for treatment with a 7-month history of slow expansion of the inferior border of the mandible. The swelling, which did not cause buccal or lingual enlargement, was painful on palpation. Paresthesia of the inferior alveolar nerve was not present. Radiographic examination showed a well-defined lytic lesion extending from the right mandibular canine to the second molar tooth. Erosion of the inferior border of the mandible was present (Fig. 4). An intraoral incisional biopsy was performed. Microscopic examination showed the presence of giant cells irregularly arranged in a mitotically inactive cellular stroma, foci of bone formation, and cystic spaces filled with blood. A diagnosis of a central giant cell granuloma with aneurysmal bone cyst formation was made, and the lesion was enucleated. In addition to the changes observed in the biopsy, microscopic examination of the enucleated specimen showed mildly cellular spindle-shaped areas with atypical osteoblasts that were associated with osteoid production (Fig. 5). The diagnosis was changed to that of a low-grade osteosarcoma and the affected segment of the mandible was resected.

Fig. 1. Elevation with infiltration of upper lip in case 1. Note ulcer on labial mucosa *(inset).*

Fig. 2. Radiographic view of case 1 shows demarcation of lesion posteriorly.

DISCUSSION

Intraosseous low-grade osteosarcoma is a rare variety of osteosarcoma. It warrants separate recognition because its prognosis, unlike that of classical osteosarcoma, is excellent. Parosteal osteosarcomas, which develop outside bone, share this excellent prognosis. Low-grade intraosseous osteosarcomas are, however, less common than the latter variety and distinguished by development within bone.[1]

Low-grade intraosseous osteosarcomas affecting the jaws are infrequently reported. Kurt et al.[3] documented two cases in the mandible and one in the maxilla; another case, with chondromyxoid fibroma-like features, was reported in the maxilla.[7] The latter case affected the right maxilla of a 24-year-old male patient who died 1 year after local excision of the neoplasm with pulmonary metastasis. The 10 low-grade intraosseous osteosarcomas reported by Bertoni et al.[2] in 1992 all involved extragnathic sites. No mention was made of low-grade neoplasms in a series of 34 osteosarcomas affecting craniofacial bones.[8] A low-grade osteosarcoma of the sphenoid bone that mimicked fibrous dysplasia was recently reported.[5] An osteosarcoma involving the mandible that was microscopically interpreted as fibrous dysplasia on both the incisional biopsy and excised specimen[4] probably

represented another example of low-grade intraosseous osteosarcoma of the jawbones. It is our contention that some of the earlier cases in which malignant change was reported in fibrous dysplasia[9] in fact represented low-grade intraosseous osteosarcoma from the onset.

The great pitfall in the diagnosis of low-grade osteosarcoma lies in the fact that it is clinically, radiographically, and microscopically distinct from benign conditions affecting bone. Accurate diagnosis is primarily based on the clinical, radiographic, or microscopic identification of an infiltrative growth pattern. In a series of 80 low-grade intraosseous osteosarcomas, poor margination was present in two thirds of cases and there was extension into soft tissue in one half of cases.[3] Seven of the 10 cases reported by Bertoni et al.[2] showed cortical violation with soft tissue invasion. Both of our cases demonstrate that although the histopathologic features favor a benign process in many microscopic fields, cortical destruction with dermal and mucosal infiltration are the most important criteria in establishing the final diagnosis. Microscopically, the infiltrative growth pattern in case 1 was reflected by the loss of the buccal bone plate and by the bone-forming lesion infiltrating the mucosa, growing around minor salivary glands rather than displacing them. Our second case, however, was well demarcated, and it exhibited sharp
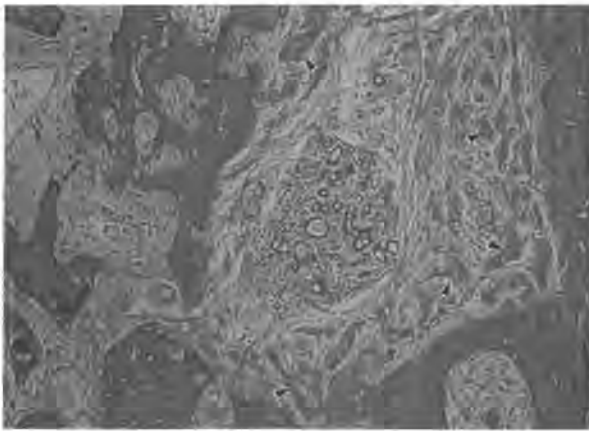
Fig. 3. Infiltration of well-differentiated bone-forming tumor around minor salivary gland in case 1; abundance of osteoid *(arrows)* can also be seen (hematoxylin-eosin, original magnification ×100).

Fig. 4. Expansion of inferior border of mandible in case 2 *(left, qrrows)*. Panoramic radiograph *(right)* shows well-defined lytic lesion with destruction of inferior border *(arrows)*.

margins, which were featured in 20% of the cases reported by Kurt et al.[3] and 3 of 10 cases in the series of Bertoni et al.[2] Violation of the inferior border of the mandible with infiltration of the dermis was present, however.

Microscopically, low-grade intraosseous osteosarcoma is essentially a spindle-cell tumor with irregular bone production, low cellularity, fewer than 4 mitoses per 10 high-power fields, and an absence of pronounced atypia. In most cases, heavy seams of irregular calcified osteoid or scattered seams of osteoid embedded in a collagen stroma with multiple vascular spaces are seen.[3] Abundant osteoid with osteoblastic rimming may mimic an osteoblastoma.[3,10] Other growth patterns include areas resembling fibrous dysplasia, desmoplastic fibroma, or fibromyxoid change.[2,7] Our second case focally showed changes compatible with a central giant cell granuloma with aneurysmal bone cyst formation on initial biopsy.

From a differential diagnostic point of view, distinction from fibrous dysplasia poses the most important problem. It is frequently not possible to make the distinction microscopically alone, and although low-grade intraosseous osteosarcomas may appear benign on radiographs, fibrous dysplasia never shows the infiltrative characteristics of a malignancy.[3] The solid areas in aneurysmal bone cysts are sometimes mistaken for low-grade intraosseous osteosarcoma. The latter is hypocellular with little mitotic activity whereas aneurysmal bone cyst shows increased cellularity and brisk mitotic activity.[1,3] The scarcity of mitotic figures in the stroma of the initial biopsy of our case 1 is an indication that the proliferation is not entirely compatible with that found in a giant cell granuloma.
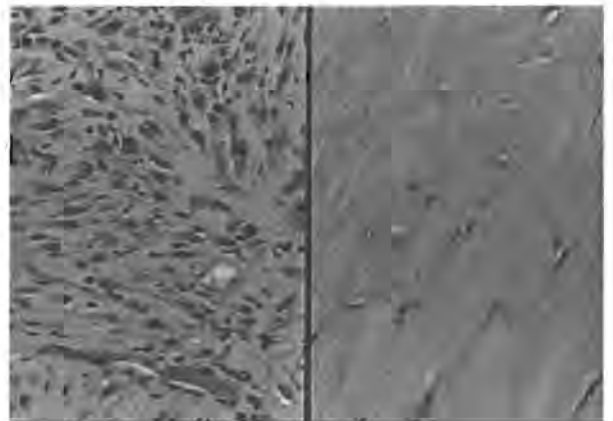

Fig. 5. Microscopic appearance of excision specimen of case 2. Note spindle-shaped growth pattern *(left;* hematoxylin-eosin, original magnification ×100). Abundant osteoid and mildly atypical osteoblasts can also be seen *(right;* hematoxylin-eosin, original magnification ×200).

Histologically there may be an overlap in the features of low-grade osteosarcoma and parosteal osteosarcoma. The latter is distinguished by its location on the surface of the bone rather than centrally and within bone.[2]

Although our cases have not been followed for a sufficient period of time, the literature makes it clear that complete removal at the first attempt is important. The transformation of low-grade intraosseous osteosarcoma into high-grade osteosarcoma at recurrence occurred in 15% of patients in the Mayo Clinic series. The course of cases with recurrent growths is reported to be similar to that of cases of high-grade osteosarcoma, and the development of metastasis correlated

with this transformation.[3] The treatment of choice is therefore wide excision with amputation if technically feasible. Lesional curettage or marginal excision should be considered to be inadequate therapy.[2,3]

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CASE REPORT

Tumoral calcinosis of the temporomandibular joint region

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A rare case of tumoral calcinosis, discovered in the medial pterygoid muscle and around the temporomandibular joint on a routine panoramic radiograph is presented. CT was found to be ideal for the determination of the exact location of the calcifications. The differential diagnosis of tumoral calcinosis is discussed.

Keywords: tumoral calcinosis; calcification, pathologic; temporomandibular joint; facial muscles

Case report

A 29-year-old Caucasian female presented for routine dental examination. A panoramic radiograph revealed a calcified mass superimposed on the upper third of the ramus of the left side of the mandible (Figure 1a). The dental practitioner interpreted the mass as an ectopic tooth which was outside the focal trough of the panoramic radiograph. The patient was referred to an oral and maxillofacial surgeon for further management. CT (Figure 1b) showed a large area of calcification, measuring 1 cm in diameter in the left medial pterygoid muscle as well as multiple smaller calcifications in both the muscle and the soft tissue medial to the temporomandibular joint. No other clinical signs or symptoms were associated with the lesions. No history of trauma could be obtained. A clinical diagnosis of metastatic soft tissue calcification was made. Normal kidney function and serum calcium, phosphate, 1,25-(OH)$_2$-vitamin D and parathyroid hormone concentrations, however, failed to confirm this diagnosis. The large calcification was removed using an intra-oral approach and submitted for pathological examination. On sectioning, the mass was found to consist of a friable, amorphous, chalky white material enclosed in a fibrous capsule. Microscopy showed the calcification to be composed of a concentric amorphous deposit of calcified material exhibiting bony metaplasia peripherally (Figure 2). A

final diagnosis of tumoral calcinosis was made. No familial history of the condition could be obtained.

Discussion

Tumoral calcinosis is a rare disorder of unknown cause first described by Duret in 1899.[1] Ghormley and McCrary[2] described a similar condition in three sisters in 1942, but the term 'tumoral calcinosis' was only introduced by Inclan in 1943,[3] who diagnosed the disorder in three Black women. The condition most frequently occurs in Black people,[4] particularly those of African descent,[3,5] and shows a slight predominance in females in the first or second decades of life. Development is rare in patients over 50 years of age.[6] Tumoral calcinosis presents with multiple calcified masses ('tumors') commonly located in periarticular regions without being connected to the associated joint.[7] Hips, elbows and shoulders are most frequently affected, the two latter areas being more prone to recurrence and aggressive behaviour. The face, fingers and knees are rarely involved.[6] Three cases have been documented in the region of the temporomandibular joint[6,8] and one in the premaxillary area.[9]

In one-third of cases tumoral calcinosis manifests as a component of an heritable metabolic disease, transmitted either as an autosomal recessive or, more likely, as an autosomal dominant with variable clinical expressivity.[10] A congenital defect in phosphate metabolism has also been suggested following a report of an associated increase in serum phosphate in siblings with the condition.[11] In our case the serum phosphate was normal. In order to avoid confusion with

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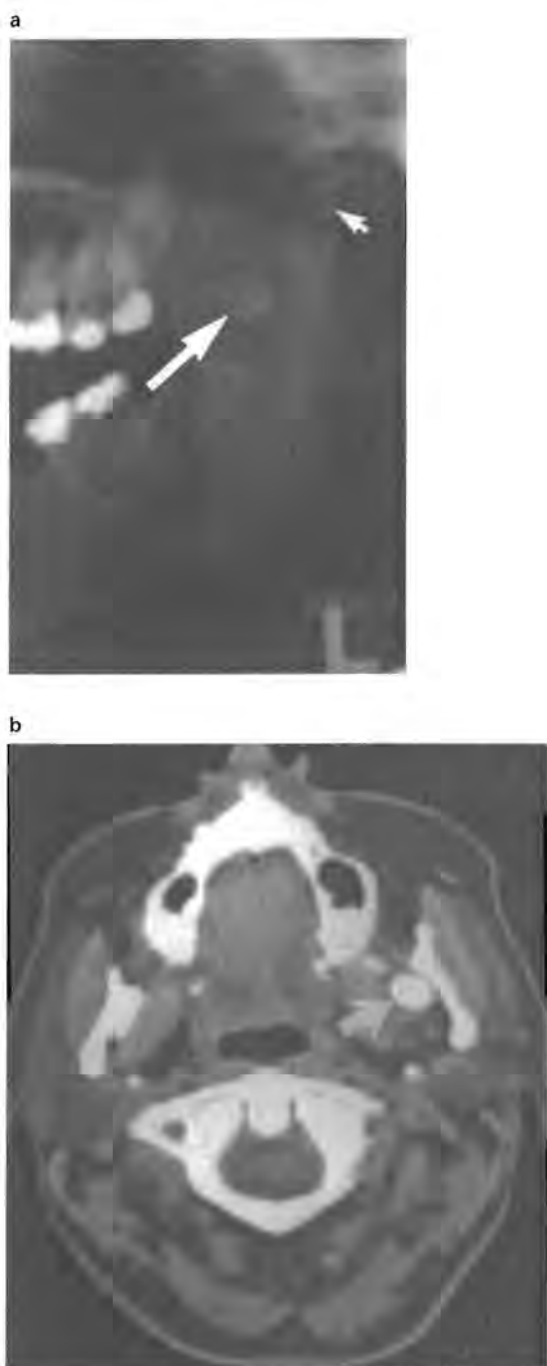Received 28 June 1999; accepted 24 November 1999

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b

Figure 1 (a) Part of a panoramic radiograph showing calcified masses superimposed on the upper third of the left mandibular ramus (large arrow) and temporomandibular joint (small arrows). (b) Axial CT scan through the left mandibular ramus showing the location of the largest calcification (arrow) and the smaller lesions both anterior and posterior to it

Figure 2 Microscopic appearance of the calcified mass (left) (H&E section, magnification × 80). Bony metaplasia was present in the peripheral part of the lesion (right) (H&E section, magnification × 200)

metastatic calcification, we agree with Zanetti[6] that the term tumoral calcinosis should be restricted to those cases in which both serum calcium and phosphate are normal. The role of local trauma with inflammation has b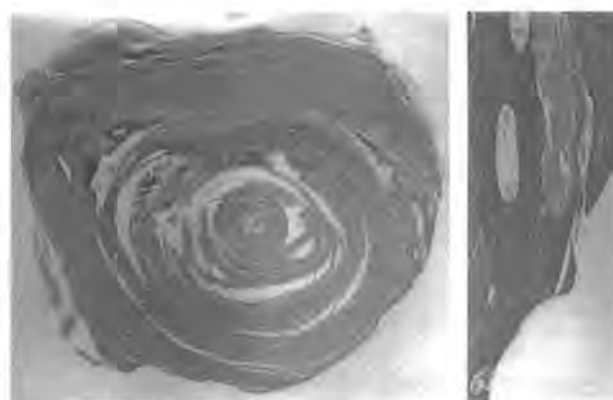een considered in the pathogenesis of tumoral calcinosis since a history of trauma and degeneration of the articular capsule was reported in a number of cases.[1,6,12] No history of trauma could be obtained in our case. Dystrophic calcification is a more appropriate term for calcified deposits secondary to tissue damage and we would discourage the use of the term tumoral calcinosis in association with a history of trauma. Gal et al[13] reported facial or intra-oral pathological changes associated with tumoral calcinosis at a very young age. These initial findings included erythematous patches and a maculopapular rash on the face and extremities, hoarseness and angular cheilitis. None of these findings were present in our case.

Tumoral calcinosis grows rapidly, sometimes appearing in a matter of months. The masses may be huge and are usually painless although pain may result during joint movement.[4] Radiographically, the lesions present as nodular peri-articular and soft tissue masses. Surgical excision is recommended in cases presenting with large lesions associated with deformities or symptoms. Incomplete excision can lead to multiple recurrences.[14]

The differential radiological diagnosis of tumoral calcinosis should include implanted foreign material, dystrophic or metastatic calcification, phlebolith, calcified haemangioma, fibrodysplasia ossificans progressiva, calcinosis cutis, gout and synovial osteochondromatosis. Implanted foreign material will be associated with a history of trauma. Dystrophic calcifications present as irregular foci of mineralization within areas of tissue degeneration in necrotising infections, malignant tumours or haemorrhage. Metastatic calcifications are associated with derangements in mineral metabolism, most notably acute hyperparathyroidism and renal failure and present as diffuse mineral deposits which have an affinity for the elastic tissue of blood vessel walls. The calcifications in phleboliths and calcified haemangiomas are associated with thrombosed vascular spaces. Fibrodysplasia ossificans progressiva is characterised by bony dyspla-

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sia of connective tissue and skeletal muscle and the mineralised deposits of calcinosis cutis are localised close to the surface of the skin. In gout, deposits of monosodium urate form within and around various joints, leading to chronic arthritis and a foreign body giant cell reaction. Synovial osteochondromatosis is an uncommon benign lesion, characterised by multiple osteocartilaginous nodules in the synovium of joints.

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