International Journal of Dentistry

Contemporary Issues in Head and Neck Pathology and Radiology

Guest Editors: Paul C. Edwards, Preetha P. Kanjirath, Tarnjit Saini, and Neil S. Norton

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Editorial

Contemporary Issues in Head and Neck Pathology and Radiology

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The comprehensive evaluation, assessment, and management of patients with non-tooth-related conditions of the head and neck area are essential aspects of the practice of dental medicine. The manuscripts selected for publication in this special issue serve to illustrate the importance of close cooperation between oral and maxillofacial pathology, radiology, oral medicine, and head and neck anatomy in both the initial diagnostic and subsequent treatment phases when evaluating and treating patients with non-tooth-related conditions of the oral and maxillofacial complex.

I would like to genuinely thank my Guest Editors, Dr. Neil S. Norton from Creighton University in Omaha, Neb, USA Dr. Preetha P. Kanjirath, from the University of Michigan at Ann Arbor, Mich, USA and Dr. Tarnjit Saini, Brooke Army Medical Center Fort Sam Houston, in San Antonio, Tex, USA for their assistance. Without their involvement and thoughtful discussions, this special issue would not have been possible. I also extend my thanks to the authors who have contributed to this special issue, as well as to the many reviewers who graciously volunteered with the peer-review process.

In the lead article in this special edition, "*Bone Diseases of the Jaws*", by P. J. Slootweg, provides an overview of the more common and/or important lesions occurring in the oral and maxillofacial complex, while emphasizing the considerable overlap in clinical, histological, and radiological features among these entities.

Y. Morimoto and colleagues review the usefulness of ultrasound imaging for the detection of noninvasive and soft tissue-related diseases and introduce three new potential applications of ultrasonography: guided fine-needle aspiration, measurement of tongue cancer thickness, and diagnosis of metastasis to cervical lymph nodes.

Subsequent manuscripts explore the relationship between craniofacial pathology and anatomy. L. Sonnesen summarizes recent studies on the link between morphological deviations of the cervical vertebral column and craniofacial morphology, while Guest Coeditor Neil S. Norton and colleagues employ volumetric tomography to review the anatomy of the greater palatine canal and also to rule out a statistically significant association between the prevalence of maxillary sinus disease and the presence of concha bullosa and/or nasal septal deviation.

R. A. Mesquita and colleagues critically review the available literature on the nonsurgical treatment of oral leukoplakia, while E. de S. Tolentino and colleagues present a well-documented case of an ameloblastic fibroma that illustrates the need to integrate radiology, oral and maxillofacial pathology, and head and neck anatomy in both the initial diagnosis and subsequent treatment of lesions of the maxillofacial complex.

On behalf of my Guest Coeditors and myself, I hope that you will find the manuscripts that comprise this special issue both interesting and informative.

Paul C. Edwards
Preetha P. Kanjirath
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Review Article

Bone Diseases of the Jaws

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Lesions specific for the jaws and not occurring in any other bones mostly are related to the teeth or to odontogenic tissues. Moreover, the jaws may harbor nonodontogenic bone lesions not seen in any other part of the skeleton. This paper pays attention to the diseases that are specific for the jaws, odontogenic as well as nonodontogenic. Both neoplastic and nonneoplastic entities will be discussed.

1. Introduction

Jaw bone differs from other bones in several aspects. Embryologically, it is unique due to its development from cells migrating from the embryonal neuroectoderm. Anatomically it houses the tooth germs. With both unique features in the jaws, diseases occur that are not seen in any other part of the skeleton. For the purpose of this paper, these will be divided in 2 main groups: those related to the dentition and those restricted to the bone proper. Tooth-related jaw bone diseases can be divided in cysts and odontogenic tumors. Reactive bone diseases, fibro-osseous lesions, giant cell lesions, and bone tumors are taken together as the main second group.

2. Cysts of the Jaws

The majority of cysts in the jaw bones are called odontogenic as they are derived from odontogenic epithelium that is related with the tooth development; only a few are nonodontogenic but have other kinds of epithelium as their source. Odontogenic cysts are classified as inflammatory and developmental. In the first group, inflammatory changes are the stimulus for epithelial odontogenic remnants to proliferate and transform into epithelium-lined cystic cavities. This means that their occurrence can be related to poor oral health. Appropriate dental care will reduce their incidence. The pathogenesis of the developmental cysts is not elucidated [1, 2].

2.1. Odontogenic Cysts: Inflammatory. Radicular cysts are located at the root tips of teeth with necrotic pulp tissue, mostly due to extensive caries. Histologically, they are lined by nonkeratinizing epithelium. The fibrous cyst wall may show a chronic inflammatory infiltrate composed of lymphocytes and plasma cells. The extent of this infiltrate may vary. A radicular cyst left behind in the jaw after removal of the associated tooth is called *residual cyst.* Cysts with the same histology as mentioned above but located at the lateral side of the tooth at the border between enamel and root cementum are called *paradental.* It is thought that they may be related to deep periodontal pockets.

2.2. Odontogenic Cysts: Developmental. Dentigerous cysts surround the crown of an unerupted tooth, mostly the maxillary canine or the mandibular third molar tooth. Usually, the cyst wall is attached at the neck of the involved tooth, forms an umbrella covering the crown part, and is lined by an epithelial lining consisting of two to three layers of cuboidal cells. These cysts may be big in size and radiologically, they can be confused with odontogenic tumors. In practice, the larger the pericoronal radiolucency, the higher the chance that it is not a dentigerous cyst but a genuine neoplastic odontogenic lesion. *Lateral periodontal cysts* are located between the roots of vital teeth. This discerns them from laterally positioned radicular cysts which are related to nonvital teeth. They are lined by a thin, nonkeratinizing squamous or cuboidal epithelium with focal, plaque-like

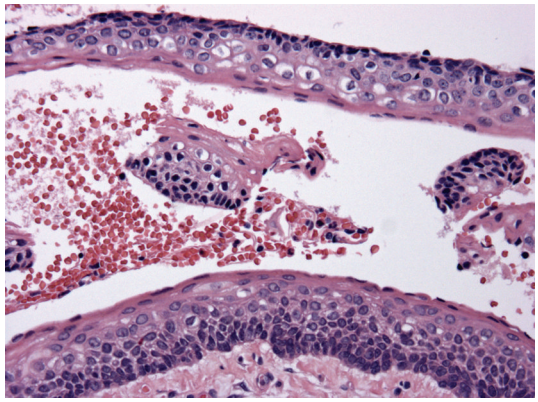

Figure 1: Picture of keratocyst showing typical epithelial lining with basal palissading and corrugating parakeratinized surface.

thickenings that consist of clear cells. Sometimes, cysts with this histological appearance occur in the soft tissues of the gingiva: then the designation *gingival cyst* is employed. *Botryoid odontogenic cysts* also have the same histology but are much larger and multilocular by radiology.

The *glandular odontogenic cyst*, also called *sialo-odontogenic cyst* shows an epithelial lining that is partly nonkeratinizing squamous, partly cuboidal or columnar with cells that can have cilia and may form papillary projections. It is important to recognize this cyst histologically as it may recur after treatment.

From a practical point of view, the only cyst for which classification goes beyond academic value is the *odontogenic keratocyst*. Histologically, this cyst differs from all other jaw cysts in showing a lining of stratified squamous epithelium with a well-defined basal layer of palissading columnar or cuboidal cells and a superficial corrugated parakeratin layer (Figure 1). The underlying cyst wall may contain tiny daughter cysts and solid epithelial nests; they are more common in cysts associated with the nevoid basal cell carcinoma syndrome [3]. Recognition is important as keratocysts tend to recur after enucleation and sometimes, a partial jaw resection is needed for cure. Because of this neoplastic behavior, the most recent WHO classification proposes the diagnostic designation *keratocystic odontogenic tumor* for this lesion [4]. Although this reclassification is based on clinical features, its rationale is supported by the demonstration of genetic alterations that are common for neoplasia such as loss of tumor suppressor gene activity and overexpression and amplification of other genes [5]. Sometimes, cysts are lined by orthokeratinized epithelium, thus having the appearance of an epidermoid cyst. They should be distinguished from the odontogenic keratocyst with parakeratinization because they lack any tendency for recurrence, thus being amenable to more limited treatment than the odontogenic keratocyst with the parakeratinizing epithelium.

2.3. Nonodontogenic Cysts. As the name already implies, these cysts are derived from other epithelial sources in the jaws or neighbouring soft tissues.

Epithelial remnants of the nasopalatine duct are the source for the *nasopalatine duct cyst*. The cyst lies in the anterior palate just behind the central incisor teeth; its lining consists of an admixture of squamous and respiratory epithelium. If one of both neighbouring central incisor teeth are nonvital, differentiation between a nasopalatine duct cyst and a radicular cyst may become impossible.

The nasolacrimal duct may give origin to the *nasolabial cysts*. This cyst is located in the soft tissue just lateral to the nose at the buccal aspect of the maxillary alveolar process. Its lining also combines squamous and respiratory elements. Due to its soft tissue location, there are no associated radiologic abnormalities.

3. Odontogenic Tumors

Odontogenic tumors comprise a group of lesions that have in common that they arise from the odontogenic tissues. As tooth germs have both an epithelial and a mesenchymal part, these tumors may be either epithelial, mesenchymal, or both.

Clinically, this group of lesions encompasses entities whose behavior varies from frankly neoplastic including metastatic potential to nonneoplastic hamartomatous. The latter may recapitulate normal tooth development including the formation of dental hard tissues such as enamel, dentin, and cementum [6]. It is obvious that a precise diagnosis is mandatory; at one hand to avoid unnecessary overtreatment in case of hamartomatous lesions with their limited growth potential and subsequent maturation, at the other hand to avoid delay in treatment of genuine odontogenic neoplasms. Due to overlapping histological features, this is not always easy.

3.1. Odontogenic Tumors: Epithelial. Ameloblastomas are among the more common odontogenic tumors. They consist of epithelial strands or of discrete epithelial islands. The cells at the border with the adjacent fibrous stroma are columnar and resemble ameloblasts, the cells that form enamel in the immature tooth. Liquefaction in the epithelial as well as in the stromal areas may cause cysts that coalesce to form the large cavities responsible for the multicystic gross appearance ameloblastomas may show. The tumor infiltrates the adjacent cancellous bone. Therefore, treatment should include removal of some adjacent healthy jaw bone to obtain tumor-free margins [7].

From the various known subtypes only the desmoplastic and the unicystic warrant further discussion. *Desmoplastic ameloblastoma* shows a dense collagenous stroma, the epithelial component being reduced to narrow strands of epithelium and within the stromal component, and active bone formation can be observed [8]. This type of ameloblastoma may be confused with a bone forming jaw lesion, especially one of the fibro-osseous group, as the bone formation in the stroma leads to a mixed radiodense-radiolucent radiological appearance. This contrasts with the radiological appearance of prototypical ameloblastomas that are homogeneously radiolucent.

Sometimes, ameloblastomas present themselves as cysts consisting of one single intraosseous cavity that is lined by

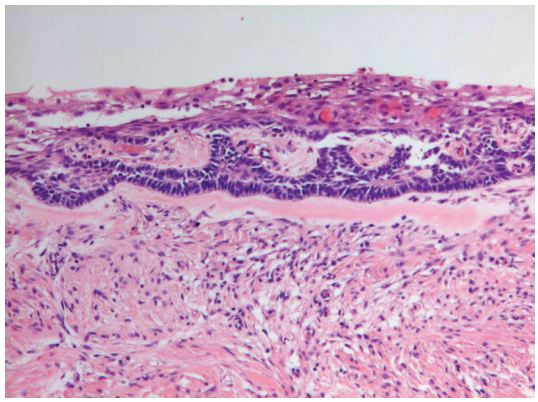

Figure 2: Unicystic ameloblastoma. Epithelial lining shows basal rim of dark staining palissading cells and subepithelial hyalinization which both are typical for ameloblastoma.

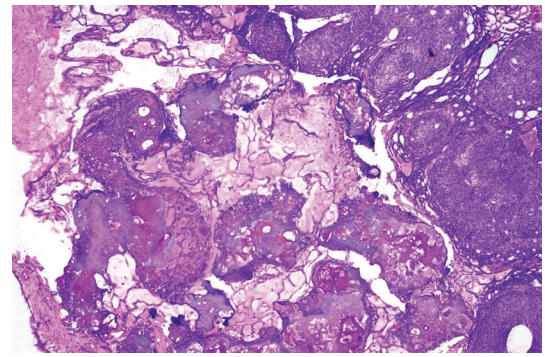

Figure 3: Adenomatoid odontogenic tumor consisting of epithelial nodules containing calcified material and interconnected with thin epithelial strands.

ameloblastomatous epithelium (Figure 2). This type is called *unicystic ameloblastoma.* If there is "dropping off" of this epithelium into the underlying fibrous cyst wall, the behavior is the same as that of the conventional ameloblastoma thus necessitating adequate surgery. The uncomplicated unicystic ameloblastoma without this mural epithelial component may be treated by simple enucleation [9]. To avoid overlooking an intramural component, extensive histological sampling of the enucleated cyst wall is required.

Less common is the *calcifying epithelial odontogenic tumor,* a lesion composed of sheets of large eosinophilic cells with pleomorphic nuclei and very conspicuous intercellular bridges. Growth characteristics are the same as for the ameloblastoma and hence, treatment also includes removal with a healthy margin [10].

Adenomatoid odontogenic tumor quite often assumes the clinical presentation of a dentigerous cyst, investing the crown part of an impacted tooth to which it is connected at the level of the cemento-enamel junction. Histologically, this tumor consists of epithelial nodules connected to each other by thin epithelial strands. Larger nodules also contain duct-like spaces lined by columnar cells and extracellular eosinophilic matrix (Figure 3). Its behavior is benign and simple enucleation is adequate treatment.

The last entity in the group of epithelial odontogenic tumors is the *squamous odontogenic tumor.* It is composed of islands of well-differentiated nonkeratinizing squamous epithelium surrounded by mature fibrous connective tissue. In the epithelial islands, cystic degeneration as well as calcification may occur. Invasion into cancellous bone may be present.

3.2. Odontogenic Tumors: Mesenchymal. Odontogenic myxomas consist of monotonous cells with a fibroblastic appearance that lie in a myxoid stroma. This histomorphology is almost identical to the dental follicle and the embryonic dental pulp, to so-called dental papilla. To avoid misdiagnosing these components of the normal tooth germ as myxoma, clinical and radiographic data are decisive [11]. As the tumor does not show encapsulation, it has to be removed including a rim of adjacent normal jaw bone to avoid recurrence [12]. So, it will be apparent that proper distinction between an immature dental pulp and myxoma is mandatory to avoid unnecessary mutilating surgery at one side or delaying the treatment needed for myxoma at the other side.

Odontogenic fibroma is a controversial entity. Uncertainty exists about the histologic spectrum that this lesion may show as well as about its separation from other fibrous jaw lesions. The lesion consists of fibroblasts lying in a background of myxoid material intermingled with collagen fibers that may vary from delicate to coarse and thus resembling the dental follicle [11, 13].

Cementoblastomas consist of a mass of cellular cementum connected with the root surface that may show signs of external resorption. In addition to the hard tissue-component, fibrous tissue with hyperplastic cementoblasts is present [14]. Cementoblastomas should not be confused with hypercementosis, an increase in thickness of the cemental layer that covers the root surface and that may be both cellular and acellular. Rarely, confusion may arise concerning the distinction of cementoblastoma from osteoblastoma; the latter is a bone tumor more common to the extragnathic skeleton. As osteoblastomas lack the firm connection with the roots of the teeth, radiographic documentation allows the differentiation between both [15]. Clinically, cementoblastomas are characterized by persistent pain which is rather unique for benign bone forming jaw lesions.

3.3. Odontogenic Tumors: Mixed Epithelial and Mesenchymal. Mixed odontogenic tumors contain both epithelial and mesenchymal tissues and may recapitulate odontogenesis in varying degrees [16].

When the lesion resembles the immature tooth germ without presence of either dentin or enamel, it is called *ameloblastic fibroma.* If there is a combination of dentin as well as enamel together with soft tissues resembling the epithelial enamel organ and the mesenchymal dental papilla, the lesion is diagnosed as an *ameloblastic fibro-odontoma* (Figure 4). In case of a rather prominent epithelial

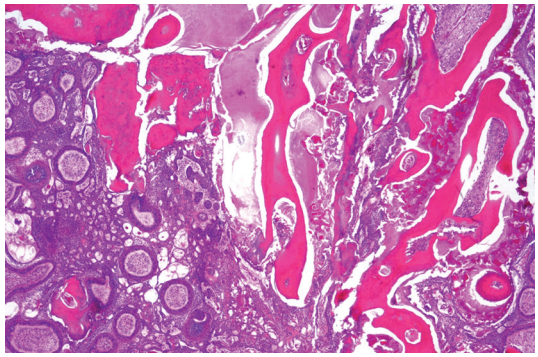

Figure 4: Ameloblastic fibro-odontoma showing ameloblastomatous epithelium, embryonal myxoid pulp tissue and dentin as well as enamel matrix.

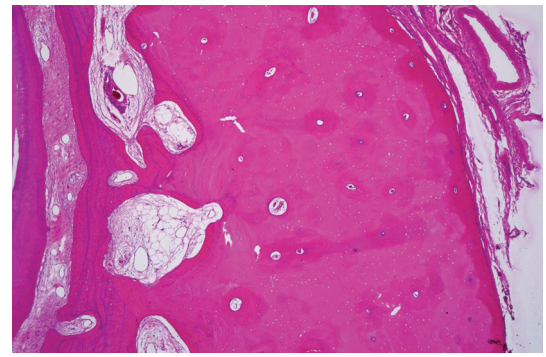

Figure 5: Alveolar tooth socket thickened due to formation of torus. The torus consists entirely of lamellar bone. At the left side the periodontal ligament space with the tooth surface are shown.

component, the ameloblastic fibroma may be confused with ameloblastoma. As the ameloblastic fibroma can be treated with simple enucleation whereas ameloblastomas require major resection, distinction between both is very important. This distinction is based on the stromal connective tissue component, immature myxoid in ameloblastic fibroma and fibrous, and mature in ameloblastoma. Radiologically, no reliable distinguishing features are present. As ameloblastomas do not contain dental hard tissue, distinction from ameloblastic fibro-odontoma does not pose major difficulties. Radiographs show a radiolucent lesion in case of ameloblastoma and a mixed radiodense-radiolucent lesion in case of ameloblastic fibro-odontoma.

If there are no immature odontogenic tissues present, lesions entirely consisting of an admixture of dentin and enamel, they are called *odontomas* [16]. In *complex odontoma,* the dental hard tissues show an haphazard arrangement; in *compound odontoma* they form tiny teeth. In a single lesion, the number of these teeth may vary from a few to dozens.

Some of the mixed odontogenic tumors mimic ameloblastoma by a predominance of an epithelial component similar to this tumor. However, they can be distinguished from ameloblastoma because of the concomitant presence of large, pale epithelial cells without a well-defined nucleus, the so-called ghost cells, and the presence of dentin. These lesions are called *calcifying cystic odontogenic tumor* when they contain a central cystic cavity and *dentinogenic ghost cell tumor* if they manifest themselves as a solid tumor mass [17, 18]. In the past, both entities were taken together under the common term calcifying odontogenic cyst or Gorlin cyst. Their distinction from ameloblastoma is important as they can be treated conservatively.

3.4. Odontogenic Tumors: Malignant. Both odontogenic epithelium as well as odontogenic mesenchyme may show neoplastic degeneration, causing either odontogenic carcinomas or odontogenic sarcomas [19]. As they all are very rare, they will be discussed very briefly, only mentioning the most important features. Within the group of carcinomas, one discerns the following entities: *malignant (metastasizing) ameloblastoma* is an ameloblastoma that metastasizes in spite of an innocuous histologic appearance. The primary tumor shows no specific features different from ameloblastomas that do not metastasize. *Ameloblastic carcinoma* is characterized by cells that, although mimicking the architectural pattern of ameloblastoma, exhibits an histomorphology indicating malignancy with the corresponding behavior: invasive growth and metastasis. The resemblance to ameloblastoma distinguishes this tumor from a *primary intraosseous carcinoma* which is a well to poorly differentiated squamous cell carcinoma arising within the jaw; not derived from the oral mucosa but probably from odontogenic epithelial remnants or an odontogenic cyst.

Odontogenic sarcomas are characterized by pleomorphic fibroblastic cells. Depending on whether they contain only soft tissues or also dentin or both dentin and enamel, they are called *ameloblastic fibrosarcoma, ameloblastic fibrodentinosarcoma,* or *ameloblastic fibro-odontosarcoma*.

4. Reactive Bone Lesions

Reactive bone lesions occur in 2 different forms. The first is the so-called *tori.* These lesions are bony outgrowths of the cortical bone (Figure 5). Mostly, they are found in the palatal midline, buccally at the maxillary alveolar ridge or both buccally and lingually at the mandibular alveolar ridge. They may hamper the applicability of dental prostheses. Otherwise, they can be left untouched, not requiring any treatment.

The second group to be mentioned under this heading is the inflammatory diseases. The presence of diseased teeth may represent a porte d'entrée for micro-organisms causing infection of the jaw bone. If bone necrosis and pus formation are predominant, one speaks of acute osteomyelitis (Figure 6). Unless the oral surgeon removes the dead bone, the disease will not heal. In case of low-grade infection, fibrosis and bone sclerosis are observed (Figure 7). This chronic osteomyelitis has to be differentiated from fibrous dysplasia or osseous dysplasia (see below for distinguishing features).

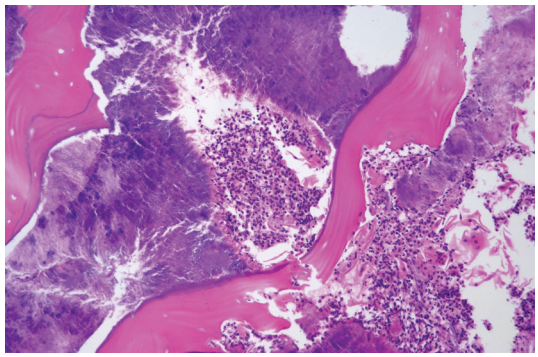

Figure 6: Acute osteomyelitis. Bony sequestrae are surrounded by colonies of bacteria as well as purulent infiltrate.

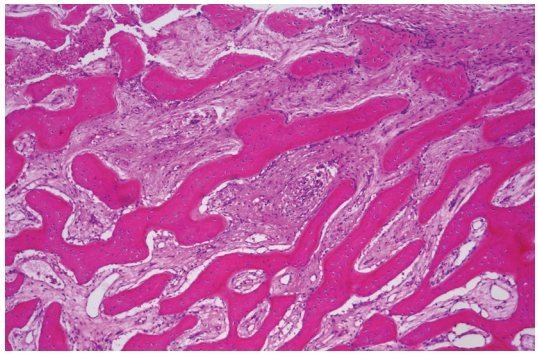

Figure 7: Chronic osteomyelitis. Parallel arrangement of lamellar bone trabeculae and intervening edematous marrow with sparse lymphocytes are typical for this disease.

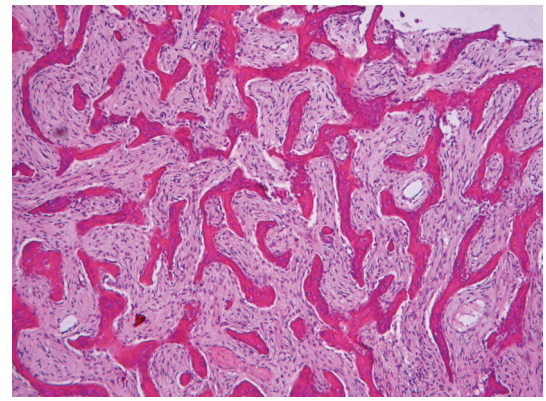

Figure 8: Fibrous dysplasia. Irregular trabeculae of woven bone lie in a monotonous fibrous stroma.

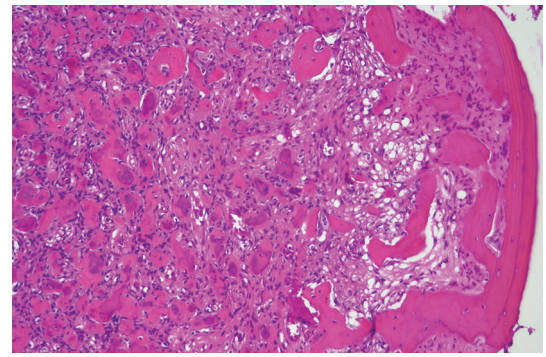

Figure 9: Ossifying fibroma, juvenile psammomatoid variant. Irregular ossicles lie in fibrous stroma. At the right side, an expanded cortical bone layer is present.

4.1. Fibro-Osseous Lesions. Fibro-osseous lesions are characterized by the presence of bone marrow that has changed into fibrous tissue and that contains mineralized material of varying appearances. Depending on the proportions of soft and mineralized tissue, they may be predominantly radiolucent, mixed radiodense-radiolucent, or mainly radiodense. Because of overlapping clinical, radiological, and histopathological features, their classification has evoked much discussion that probably will continue. Their current classification recognizes fibrous dysplasia, ossifying fibroma, and osseous dysplasia [20]. *Fibrous dysplasia* occurs in three clinical subtypes: monostotic which affects one bone, polyostotic which affects multiple bones, and Albright's syndrome in which multiple bone lesions are accompanied by skin hyperpigmentation and endocrine disturbances. Histologically it is composed of cellular fibrous tissue containing trabeculae of woven bone (Figure 8). Activating missense mutations of the gene encoding the α subunit of the stimulatory G protein are a consistent finding in the various forms of fibrous dysplasia. This genetic feature of fibrous dysplasia probably will be the convincing argument against the opinion that fibrous dysplasia and ossifying fibroma (to be discussed next) are merely opposite ends of a clinical and radiological spectrum that encompasses one single entity [21].

Ossifying fibroma, formerly also called *cemento-ossifying fibroma*, is composed of fibrous tissue that contains woven as well as lamellar bone and acellular mineralized material resembling cementum. Its circumscribed nature and variation in cellularity and types of mineralized tissues distinguishes ossifying fibroma from fibrous dysplasia as does the absence of the specific genetic alteration occurring in the latter and mentioned above.

Recently identified subtypes of ossifying fibroma are *juvenile trabecular* and *juvenile psammomatoid ossifying fibroma*. The former shows bands of cellular osteoid together with slender trabeculae of plexiform bone lined by a dense rim of enlarged osteoblasts. This lesion may be confused with osteosarcoma. Its favoured site is the upper jaw. The latter is characterized by small ossicles resembling psammoma bodies, hence its name (Figure 9). This type usually is located in the walls of the sinonasal cavities but sometimes can be encountered in the mandible [22].

Osseous dysplasia occurs in 3 different clinical forms. *Periapical osseous dysplasia* occurs in the anterior mandible and involves only a few adjacent teeth. A similar limited lesion occurring in a posterior jaw quadrant is known as *focal osseous dysplasia. Florid osseous dysplasia* is larger, involving 2 or more jaw quadrants and *familial gigantiform cementoma* involves multiple quadrants while being expansile. This latter

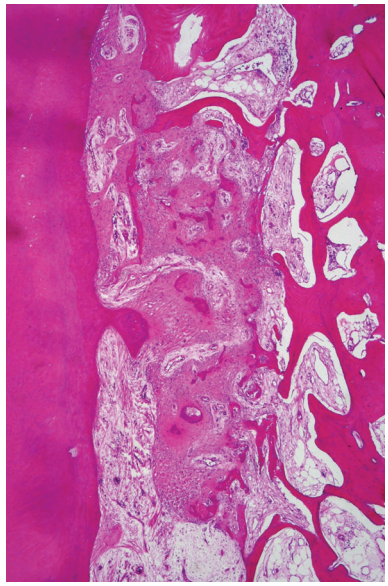

Figure 10: Osseous dysplasia. Between root surface (left) and alveolar socket (right) the periodontal ligament shows the presence of irregular bony particles.

type of osseous dysplasia shows an autosomal dominant inheritance. All 3 subtypes have the same histomorphology: cellular fibrous tissue, trabeculae of woven as well as lamellar bone, and spherules of cementum-like material (Figure 10) [23]. The immature form of periapical osseous dysplasia radiologically shows a periapical radiolucency. This should not be interpreted as periapical disease necessitating endodontic treatment. Vitality tests will be of diagnostic value in making the right decision, nonvitality in case of periapical disease and vitality in case of periapical osseous dysplasia. This point especially concerns the mandibular frontal teeth.

4.2. Giant Cell Lesions. Central giant cell granuloma and *cherubism* both show osteoclast-like giant cells lying in a fibroblastic background tissue that may vary in cellularity from very dense to cell-poor (Figure 11). The giant cells mostly cluster in areas of haemorrhage but they also may lie more dispersed among the lesion. Giant cell granuloma and cherubism are distinguished by the younger age of occurrence and the involvement of two or more jaw quadrants by the latter. Moreover cherubism has a genetic etiology, the responsible alteration having been localized to chromosome 4p16.3 [24].

The expansion of the affected jaw areas causes the angelic face leading to the lesion's designation: cherubism. With the onset of puberty, the lesions loose their activity and may mature to fibrous tissue and bone. Treatment of cherubism consists of cosmetic recontouring the maxillofacial bones if needed for cosmetic reasons. For persistent or recurrent giant cell granuloma there are some indications that treatment with calcitonin may be beneficial [25].

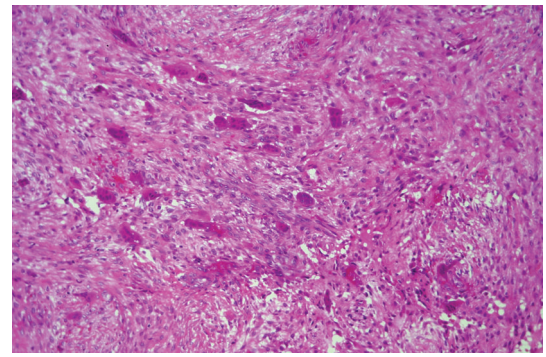

Figure 11: Cherubism: osteoclast-like giant cells lie in a fibroblastic background. Central giant cell granuloma shows an identical picture; therefore distinction between both is made on clinical and radiological grounds.

5. Conclusions

This overview of lesions in the jaw bones illustrates the huge variety occurring at this site. The clinician who is responsible for diagnosis and treatment of patients with jaw swellings should realize that quite often, there is considerable overlap in both clinical, histological, as well as radiological features. Diagnostic errors can have big consequences by causing inappropriate therapy, either too extensive or too limited. Moreover, dental and periodontal infections may both mimic or hide more serious afflictions of the jaw. Therefore a good assessment of dental and periodontal status is the first step in evaluation of patients with any jaw disease.

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Review Article

Advanced Clinical Usefulness of Ultrasonography for Diseases in Oral and Maxillofacial Regions

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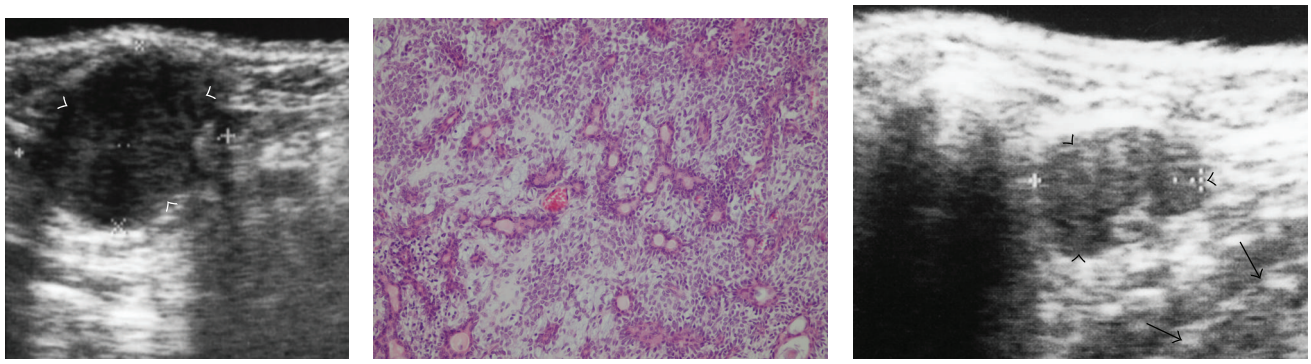
Various kinds of diseases may be found in the oral and maxillofacial regions and various modalities may be applied for their diagnosis, including intra-oral radiography, panoramic radiography, ultrasonography, computed tomography, magnetic resonance imaging, and nuclear medicine methods such as positron emission tomography. Of these modalities, ultrasound imaging is easy to use for the detection of noninvasive and soft tissue-related diseases. Doppler ultrasound images taken in the B-mode can provide vascular information associated with the morphology of soft tissues. Thus, ultrasound imaging plays an important role in confirming the diagnosis of many kinds of diseases in such oral and maxillofacial regions as the tongue, lymph nodes, salivary glands, and masticatory muscles. In the present article, we introduce three new applications of ultrasonography: guided fine-needle aspiration, measurement of tongue cancer thickness, and diagnosis of metastasis to cervical lymph nodes.

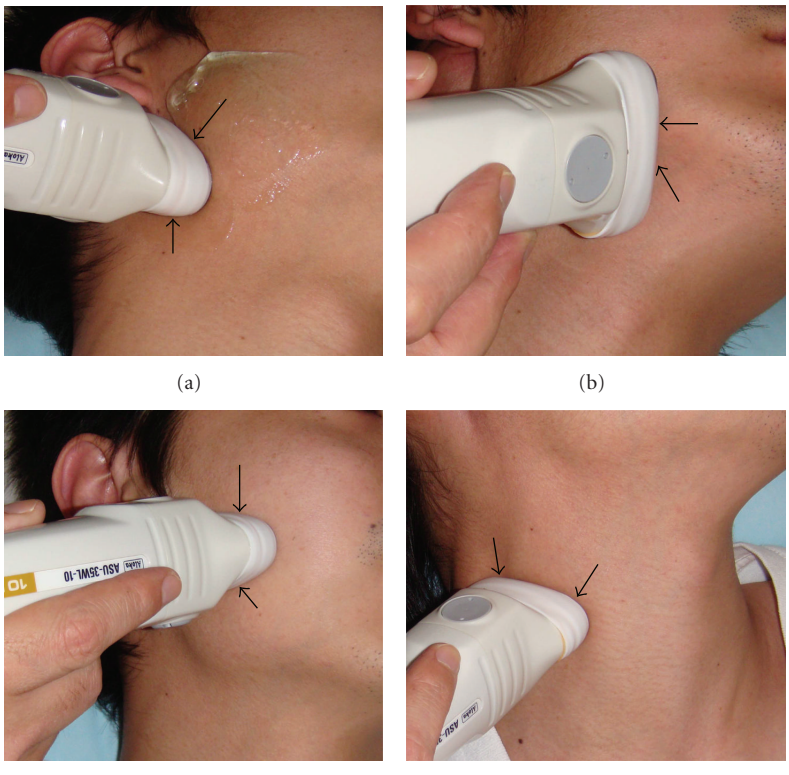
1. Introduction

Ultrasonography (US) is easy to use for the detection of noninvasive and soft tissue-related diseases in oral and maxillofacial regions [1–4]. In ultrasound images, the B-mode shows the anatomical surface structures of soft tissues (Figures 1–3) and is commonly applied for the detection of various kinds of diseases in oral and maxillofacial regions. The ultrasound image indicates the surface structures of computed tomography (CT) and magnetic resonance (MR) images (Figure 3). Recently, Doppler ultrasound images using the Doppler effect of flow in blood vessels have also been applied to evaluate the presence or absence of vascular flow in normal tissues and in diseases of the oral and maxillofacial regions. Therefore, Doppler images associated with the B-mode can provide vascular information associated with the morphology of soft tissues [5–7]. Thus, US plays an important role in analyzing normal and abnormal anatomical structures (Figure 1). In particular, in the oral and maxillofacial regions, US may be clinically applied to evaluate salivary gland-related diseases, lymph node-related diseases, subcutaneous diseases, and tongue-related diseases [8]. However, most dentists do not know the utilities of US for the diagnosis of various kinds of oral diseases and it is very disadvantageous for patients with any of the diseases mentioned above. In the present article, therefore, we explain the significance of the clinical applications of US-guided fine-needle aspiration (FNA), ultrasound identification and measurement of tongue cancer thickness, and ultrasound-based diagnosis of metastasis to



(a) (b) (c)

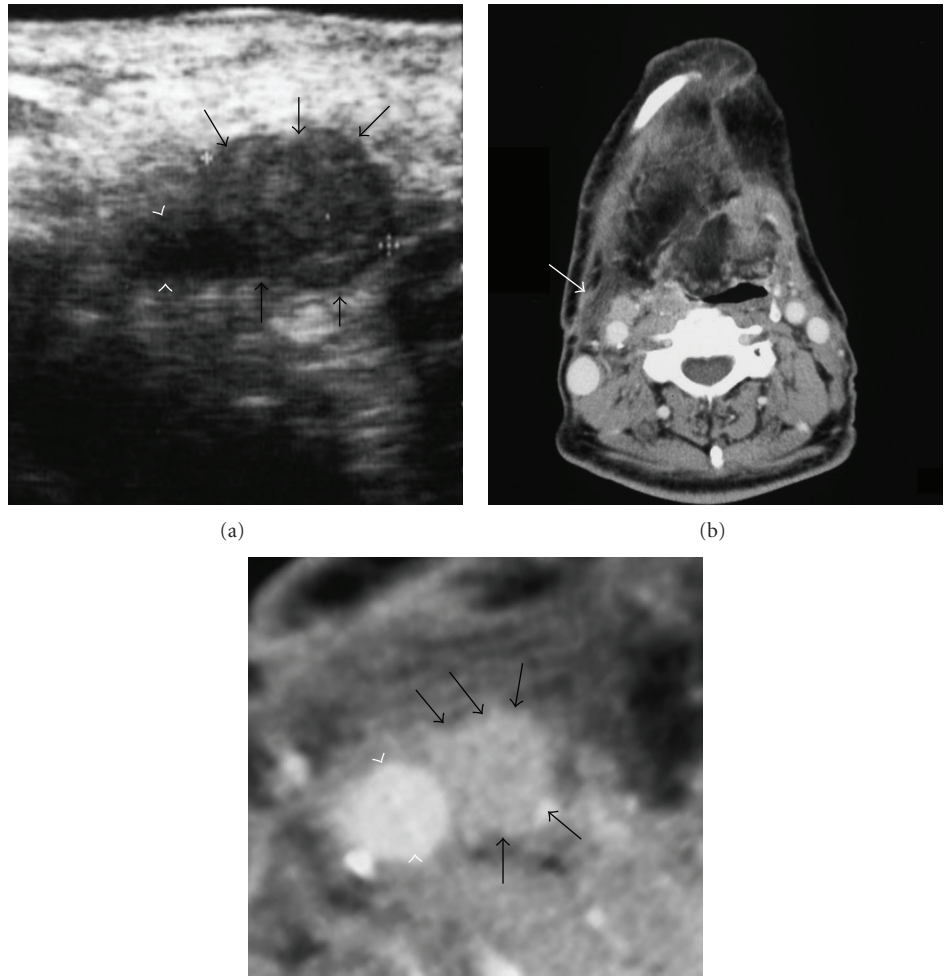
Figure 1: (a) B-mode in ultrasonography of a 58-year-old man with a pleomorphic adenoma in the left submandibular gland. The arrowheads indicate the mass lesion with an echogenic signal and a clear margin in the left submandibular gland. We diagnosed the mass clinically as a benign submandibular-related tumor. (b) A pathological specimen of the mass lesion in Figure 1(a). An area showing a mixture of epithelial and spindle-shaped myoepithelial elements in a variable background stroma that may be mucoid, myxoid, cartilaginous, or hyaline on the specimen. The specimen was diagnosed as a pleomorphic adenoma. (c) B-mode in ultrasonography of a 54-year-old woman with chronic lymphadenitis in the submandibular space. The arrowheads indicate the mass lesion with an echogenic signal and a clear margin in the submandibular space; the arrows indicate normal submandibular gland tissue. We clinically diagnosed the mass as chronic lymphadenitis.



(a) (b)

(c) (d)

Figure 2: Photographs of an ultrasonographic examination of areas in the oral and maxillofacial regions. (a) The ultrasonographic probe (arrows) directly contacted the skin over the parotid gland in the coronal angle. (b) The ultrasonographic probe (arrows) directly contacted the skin over the submandibular gland in the coronal angle. (c) The ultrasonographic probe (arrows) directly contacted the skin over the masseter muscles in the axial angle. (d) The ultrasonographic probe (arrows) directly contacted the skin over the superior internal jugular vein in the axial angle.



(a) (b) (c)

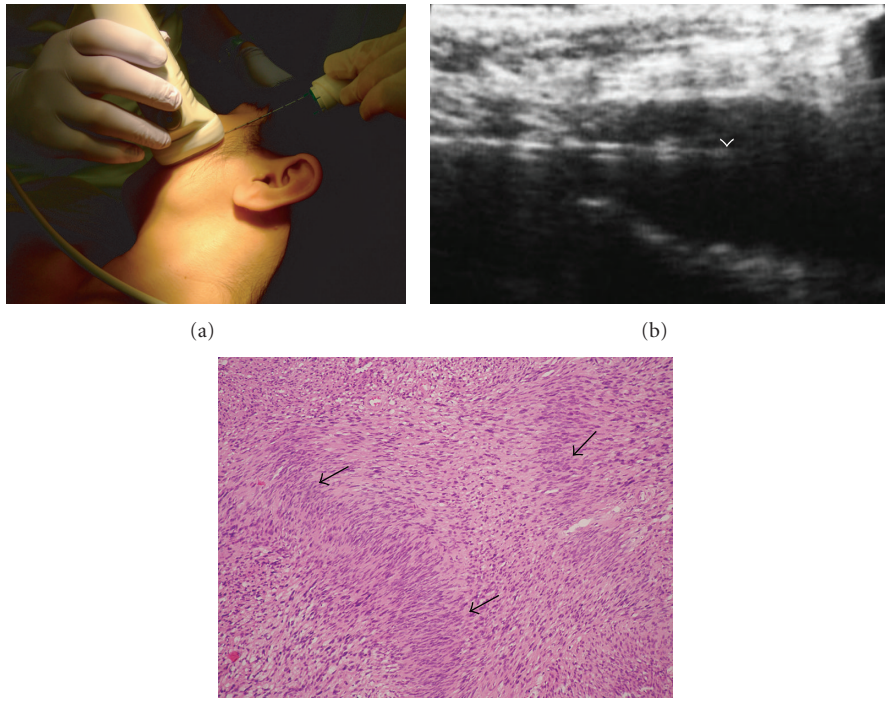
Figure 3: (a) B-mode in ultrasonography around the right superior internal jugular vein of a 69-year-old man with carcinoma on the right side of the tongue. The metastatic lymph node (arrows) contacts the common carotid artery (white arrowheads). (b) Computer tomography (CT) images of the same patient shown in Figure 3(a). The arrow indicates the same regions of B-mode in ultrasonography. (c) Magnification of CT images in area around arrow of Figure 3(b). The metastatic lymph node (arrows) contacts the common carotid artery (white arrowheads).

cervical lymph nodes based on the knowledge from various manuscripts acquired through the search engine "PubMed" (search words: ultrasonography oral and maxillofacial, ultrasonography FNA, and ultrasonography tongue).

2. Clinical Applications of Ultrasound Images in Fine-Needle Aspiration Biopsy

Ultrasound images using B-mode can precisely visualize normal and abnormal anatomical structures and can clearly identify the presence or absence of mass-like lesions in oral and maxillofacial regions. Therefore, US examination can readily detect and diagnose salivary gland- and lymph node-related diseases (Figure 1) and is a very useful tool for FNA biopsy (FNAB). In the B-mode of US examination of oral and maxillofacial regions, the ultrasound probe directly contacts the skin over the target examination areas at various angles, as indicated in the photographs in Figure 2.

Since Martin and Ellis first used the technique in 1930, FNAB has been clinically applied for the histologic evaluation of cervical masses [9]. FNAB is an inexpensive, rapid, and relatively accurate diagnostic method for many kinds of diseases in the oral and maxillofacial regions [10–16]. At the same time, various imaging modalities such as US, CT, and MR may also be used for the detection of lesions and for examinations that safely avoid disturbing important blood vessels and organs. Of these modalities, US imaging is the easiest to use, the least expensive, and the least invasive [12–14]. In addition, the accuracy of US-guided FNAB has been shown to be relatively high despite being noninvasive [12–16]. Al-Khafaji et al. reported that needle aspiration of parotid masses at a major referral cancer center had a sensitivity of 82%, a specificity of 86%, and an overall diagnostic accuracy of 84% using 154 parotid gland masses [14]. Studies have reported that the pathological diagnoses of lesions obtained using US-guided FNAB agreed with the



(a) (b)

(c)

Figure 4: (a) View of ultrasonography-guided fine-needle aspiration biopsy including cutting-needle biopsy of the left masseter muscle in a 53-year-old woman with neurilemoma using the newly developed Monopty biopsy instrument. (b) An ultrasound image showing successful centesis (arrowhead) of the needle into the mass suspected to be a neurilemoma. (c) Antoni type A areas showing nuclear palisading (arrows) on the specimen. The specimen was diagnosed as a neurilemoma.

final pathological diagnoses after surgical dissection in about 90% of 37 cases [15, 16]. Therefore, we applied US to guide FNAB for the diagnosis of cervical masses, such as those in metastatic lymph nodes, and salivary gland-related masses.

However, in about 10%–20% of cases, adequate pathological specimens could not be obtained. There have been few reports of major complications, but hematomas have been reported [10, 17]. We applied the B-mode of US for the detection of many kinds of blood vessels because color Doppler US was not available in our dental hospital (Figure 3). We have not yet experienced significant complications from the injury of vasculature in performing US-guided FNAB and have still detected vasculature using the B-mode of US without color Doppler sonography (Figure 3). If color Doppler US is available before a biopsy, routine use of color Doppler US has been encouraged to guide the cutting needle to areas of the lesion showing sufficient vascularity [18].

When performing US-guided FNAB as part of the preoperative assessment of head and neck lesions, including diagnosing lymph node metastases, we have used the newly developed Monopty biopsy instrument (MBI) (Monopty, Bard Urologic Division; Covington, GA, USA) (Figure 4(a)) [8]; few of the pathological samples obtained with this instrument had crush artifacts, injuries to the tissues caused during excision by the rushed movement of biopsy instruments, or were obscured by blood; all of which are problems that are commonly associated with manual biopsy techniques. We used the Monopty biopsy instrument to prick a mass percutaneously (Figure 4(a)) and successfully achieved centesis (arrowhead) of the needle into the mass, apparent from the ultrasound image (Figure 4(b)). The specimen in the Monopty biopsy instrument was subsequently pathologically examined and a conclusive diagnosis was reached (Figure 4(c)).

3. Interventional Radiology Using Fine-Needle Aspiration by Ultrasonography

We have injected OK-432 (picibanil), a biological response modifier used for sclerotherapy, into masses as nonsurgical treatment for ranulas in the oral floor [19–23]. Roh and Kim reported total or nearly total shrinkage in six of nine cases of ranulas [21]. In a followup after the last sclerotherapy, recurrence of the ranula was observed in only one patient [21]. No significant complications were observed; four patients reported fever and mild local pain lasting for 2–4 days after treatment [21]. Others reported that seven (33%) of 21 patients with plunging ranulas showed total shrinkage and resolution [22]. This technique using US seems to be effective for OK-432 administration to masses as a non-surgical treatment for ranulas in the oral floor [19–24].

In performing OK-432 treatment in our dental hospital, we apply US images both for confirmation of the appropriate removal of cystic fluid from the ranula (Figure 5(a)) and

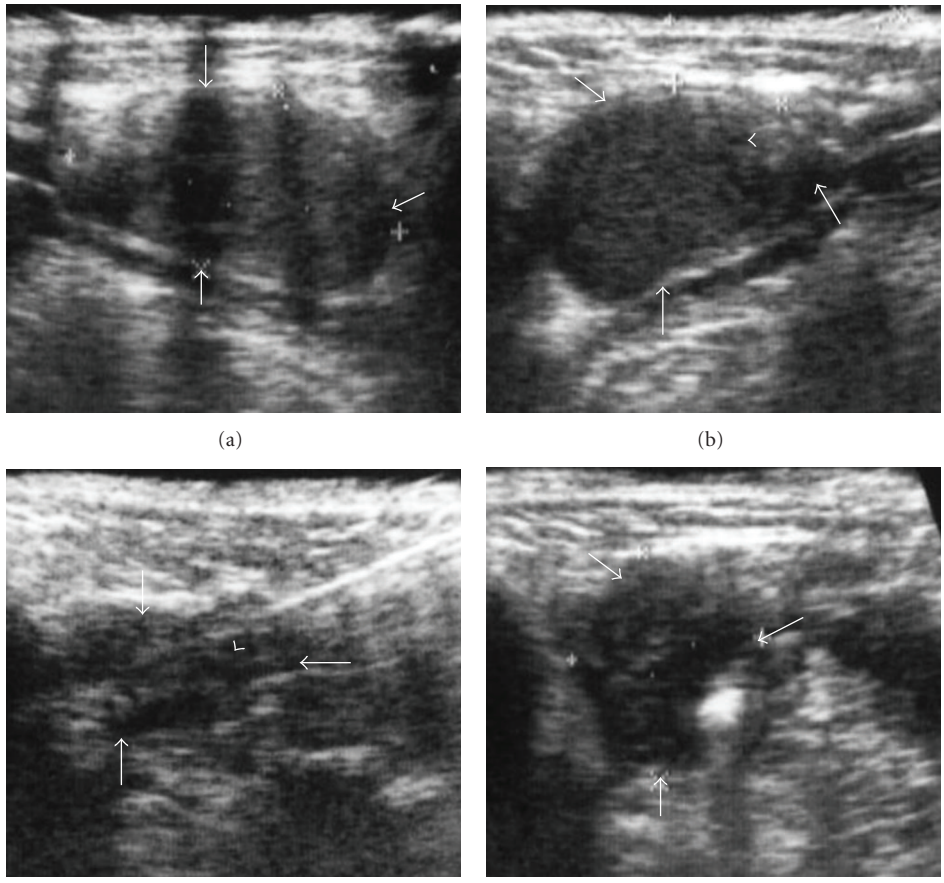
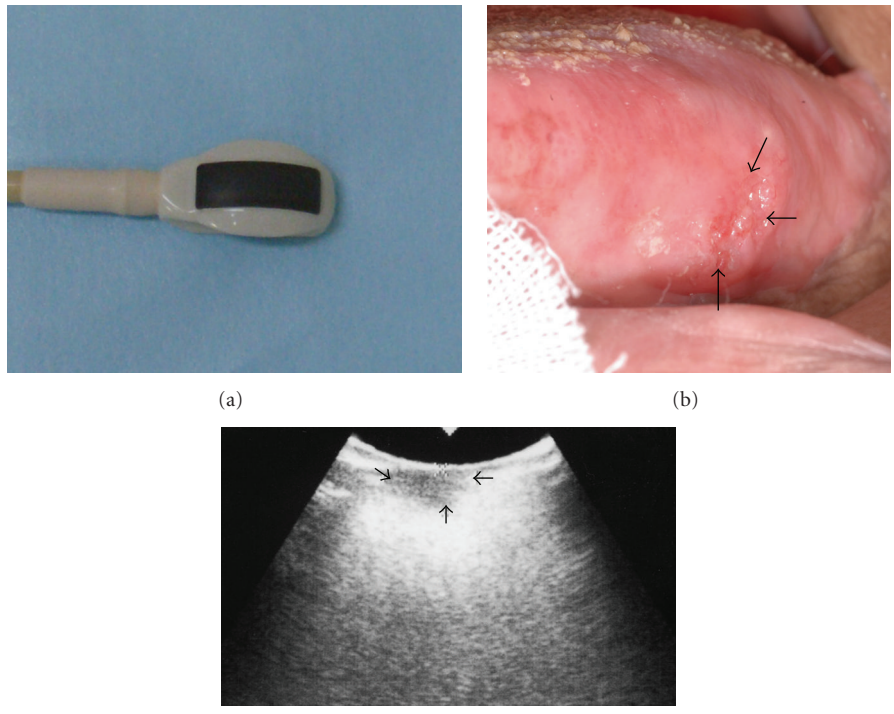


Figure 5: (a) An ultrasound image showing a mass in the right ranula of a 10-year-old girl. (b) An ultrasound image showing the successful penetration of a needle (arrowhead) in a syringe into the ranula (arrows). (c) An ultrasound image showing the decreasing mass (arrows) by aspiration using a syringe. The arrowhead indicates the needle. (d) An ultrasound image showing the increasing mass (arrows) by administration of OK-432 using a syringe.

for confirmation of OK-432 administration into the ranula (Figure 5(b)). We confirm that the end of the needle penetrates the ranula and observe that the mass decreases gradually by removal of the cystic fluid from the mass (Figure 5(c)). We also confirm that the end of the needle is repositioned into the mass and observe that the mass increases gradually by the administration of OK-432 into the mass (Figure 5(d)).

4. Clinical Applications of Ultrasound Images in the Diagnosis of Primary Lesions of the Tongue

It is very apparent that tumor thickness in oral squamous cell carcinoma of the tongue is highly related to the occurrence of cervical metastasis. Accurate preoperative assessment is indispensable to improve therapeutic effects. Particularly in cases of tongue cancer, US imaging is often used to accurately estimate tumor size or thickness and to define adequate resection margins with tumor extension and deep infiltration [25–31]. The method for estimating tongue cancer thickness involves direct contact with the tumor by a small US probe of 1×2.7 cm (Figure 6). In our dental hospital, intra-oral US of the tongue is typically performed with a 7.5 MHz linear array transducer of 1×2.7 cm (Aloka, Tokyo, Japan) (Figure 6(a)). Using this method, we have elucidated that intra-oral US offers the most exact assessment of tongue tumor thickness [29–31]. In our previous reports, we have demonstrated that the accuracy of tongue tumor thickness could be measured within 1 mm with intra-oral US [29–31]. Shintani et al. [32] showed the superiority of US over CT and MRI for its ability to measure tumor thickness within 1 mm using 24 patients and pathological specimens, and Yuen et al. [33] concluded that US was an accurate assessment modality for preoperative measurements of tumor thickness using 54 patients and pathological specimens. Additional studies have similarly reported the exact assessment of tongue tumor thickness using intra-oral US [25–33]. However, this technique using intra-oral US might provide incorrect results for the assessment of tumor thickness when the US probe cannot contact the lesion appropriately (Figure 7). In most of these cases, the tongue tumors are too large for the size of US probe (about 1×2 cm) and the size disparity between



(a) (b)

(c)

Figure 6: (a) View of the probe for intra-oral ultrasound examination. (b) View of the tumor in a 65-year-old man with carcinoma (arrows) on the left side of the tongue. (c) An ultrasound image showing the precise thickness of the tumor on the left side of the tongue (arrows) using intra-oral ultrasonography.

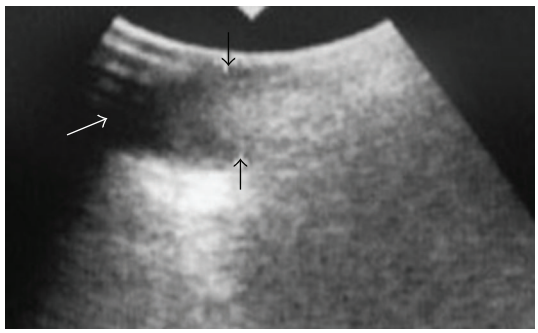


Figure 7: View of the imperfect examination (white arrow) using intra-oral ultrasonography because the tumor is located near the base of the tongue in a 67-year-old man with carcinoma (arrows) on the left side of the tongue.

the tumor and the probe makes appropriate contact difficult. Both US probe and tongue tumors are convex shapes. In particular, when tongue tumors are located near the base of the tongue, the US probe cannot reach these tumors.

Very recently, we developed and confirmed a method to easily allow operators to assess and confirm the surgical clearance of tongue carcinomas intraoperatively using intra-oral US (Figure 8) [29, 31]. Briefly, the tip of the needle was placed approximately 10 mm from the deepest portion of the tumor invasion front, with the deep surgical clearance distance verified with live ultrasound monitoring (Figures 8(a) and 8(b)). Resection was performed using the elastic needle as a landmark to show the deep surgical clearance of 10 mm (Figure 8(c)). Immediately after resection of the tumor with the maximum possible safety margin clearance, a fresh specimen was embedded in a gelatin solution. After solidification of the gelatin-embedded specimen within 10~20 minutes, direct US observation of the sample, including the tumor in the gelatin-embedded specimen, was performed (Figure 8(d)). Based on the imaging findings on the extent of resection around the tumor by US for the sample, we could decide whether additional resection around the tumor in the tongue was necessary (Figure 8(e)). The total time for the present technique was within 30 minutes and we could clinically apply this technique during real surgical procedures for tongue tumors. Using this new technique, we can safely, precisely, and subjectively decide the resection areas of tumors [29, 31]. If an inadequate margin is encountered in some portions, additional resection can be performed immediately during the same operation. Therefore, in a previous report of 13 cases with T1N0 (4 cases) and T2N0 (9 cases) tongue squamous cell carcinoma, we evaluated the significance of the technique using pathological specimens after resection as the gold standard [31]. Our technique showed a high degree of reliability in comparison with the histologic measurements for tumor thickness, because the mean difference between them was 1.21 mm, which indicated a good correlation and no underestimation

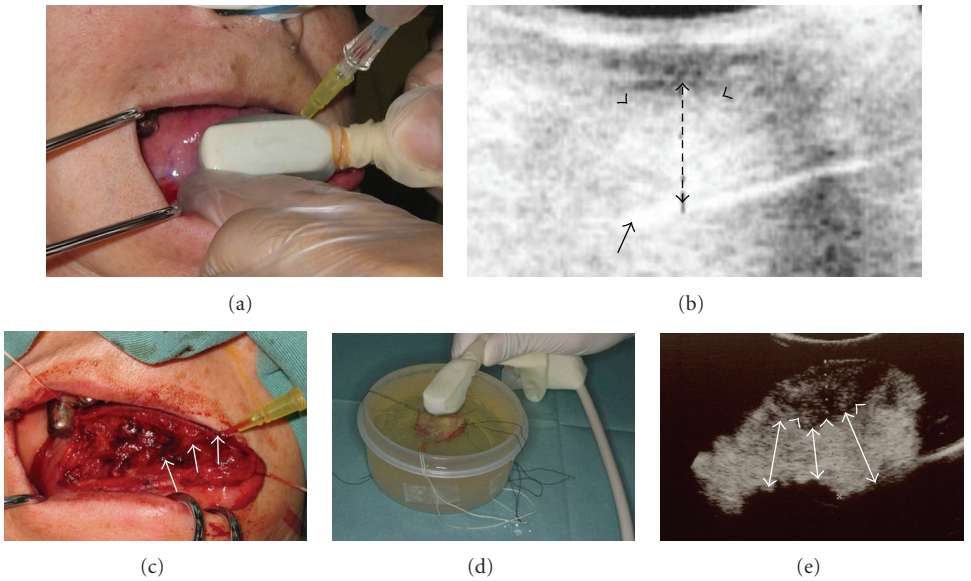


FIGURE 8: Intraoperative determination methods of tumor thickness and resection margin in tongue carcinoma using ultrasonography. (a) A view of the needle placed approximately 10 mm from the deepest portion of the tumor invasion front, with the deep surgical clearance distance verified with live ultrasound monitoring. (b) An ultrasound image of Figure 8(a). The image demonstrating the needle (arrow) placed approximately 10 mm (dotted arrows) from the deepest portion of the tumor invasion front (arrowheads). (c) Resection was performed by the use of an elastic needle (arrows) as a landmark to show the deep surgical clearance of 10 mm. (d) After solidification of the gelatin-embedded specimen, the sample including the tumor in the gelatin-embedded specimen was directly observed by US. (e) An ultrasound image of the sample in Figure 8(d) indicating the appropriate resection placed approximately 10 mm (arrows) from the deepest portion of the tumor invasion front (arrowheads).

in any case. Because there was no tumor recurrence, we speculated that there was no remnant of the tumor in the tongue after the surgical resection of the tumor in all cases [31]. In addition, in all cases, tumors had been perfectly excised based on findings on the pathological specimens after the surgical resection of the tongue tumors [31]. Kodama et al. suggested that this technique provided a definitive physical reference during resection and could be performed easily with minimal tissue distortion [31].

5. Clinical Applications of Ultrasonography in the Diagnosis of Metastatic Lymph Nodes in Oral Cancer

US can be used to assess lymph nodes in patients with oral cancers. Many studies have reported the usefulness of US for the diagnosis of lymph node metastases [34–39]. In these reports, ultrasound scanning had a diagnostic accuracy rate of about 90% in cervical lymph node staging [37] and US was significantly better than CT in depicting metastatic cervical nodes using 209 cervical lymph nodes from 62 patients and pathological specimens [39]. Furthermore, the accuracy rate for the diagnosis of metastatic lymph nodes ranged from 75% to 85%. Our experience has shown that it is very useful to evaluate the presence or absence of cervical lymph node metastasis of oral cancer after patients have undergone surgical treatment and/or radiotherapy. In regions that have been excised and exposed to radiation, in addition to the disappearance of the primary tumor, normal tissues are replaced with a cicatrix produced by granulation tissues. Furthermore, the cutaneous and subcutaneous tissues are difficult to palpate. Therefore, the diagnosis of metastases by direct palpation of the remaining lymph nodes in the neck becomes more difficult after cancer treatment. Thus, US is becoming increasingly more useful for detecting subclinical lymph node metastases. Doppler US evaluates the vascular pattern of nodes and helps to identify the malignant nodes [40, 41]. Normal lymph nodes have extensive vascularity originating in the hilus and branching radially towards the periphery [41, 42]. Conversely, the metastatic lymph nodes have peripheral vasculature that runs along the periphery of nodes and no vasculature around the hilus [41, 42]. We can easily distinguish the differences between the particular ultrasound findings of the two. According to some reports, after irradiation, the enhanced Doppler signals contribute to better visualization of the vessels and better detection of any vascular abnormalities based on a comparison between pathological and ultrasonographic findings [43, 44]. Thus, particular attention should be paid to followup imaging examinations of patients with oral cancers before and after radiotherapy to detect lymph node metastases [43].

When surveying the metastasis in cervical lymph nodes in patients with oral cancer, we suggested the clinical significance of additional ultrasonographic examination for thyroid glands [45]. In that report, we elucidated that over 30% of patients with oral squamous cell carcinoma have a relatively high rate of abnormal findings in the thyroid

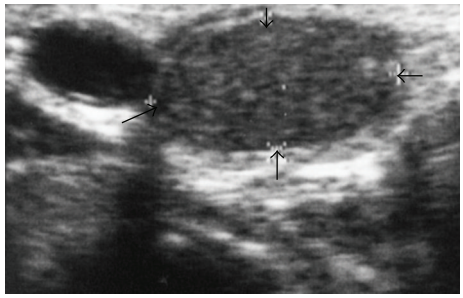


Figure 9: Ultrasound images in the right half of the thyroid gland of an 81-year-old man with squamous cell carcinoma on the right side of the tongue and metastasis in one of the superior internal jugular lymph nodes. A 2.6-cm echogenic mass (arrows) in the right half of the thyroid gland is shown.

gland that can be detected by US. In addition, as subject age increased, the rate of detection of abnormal thyroid gland findings on US significantly increased; this increase was particularly prominent for men. In one case, a 2.3-cm echogenic mass in the right side of the thyroid gland was detected in a patient with a lesion on the right side of the tongue that was diagnosed as squamous cell carcinoma by biopsy in another hospital and one metastatic lymph node was also determined (Figure 9). Moreover, particular attention should be paid to thyroid gland abnormalities if patients had oral squamous cell carcinoma on the floor of the mouth or in the maxillary gingiva. Moreover, a relative high rate of patients showed enlargement in the size of the lesion upon followup examination with US. Therefore, when such findings appeared during followup examinations, we promptly instruct patients to consult specialists to further search for lesions in the thyroid gland.

In our other study, we recommended 4–6 times per neck as one standard axial scanning period for the survey of cervical lymph nodes including the thyroid gland by US in patients with oral squamous cell carcinoma (Wakasugi-Sato et al. (submitted for publication)). In addition, beginning users of US for the detection of cervical lymph nodes should take care not to overlook accessory spinal lymph nodes.

6. Conclusions

In the present review, we described the clinical application of ultrasonography (US) for the diagnosis of various diseases in oral and maxillofacial regions, including the introduction of new trials of US such as FNA using US, the decision of surgical margins of tongue cancer lesions using US, and the clinical necessity of examination for thyroid gland-related diseases when surveying the diagnosis of cervical metastasis of lymph nodes by US.

US is easy to use for the noninvasive detection of soft tissue-related diseases in oral and maxillofacial regions. Therefore, B-mode using a relative large probe with 7.5~10 MHz should be preferentially selected for the differential diagnosis of soft tissue surfaces including salivary gland- and lymph node-related diseases. Conversely, B-mode using a small probe with 7.5~10 MHz should be applied to determine the presence or absence of tongue mass-like lesions, including benign or malignant tumors, of the tongue. In addition, the modality is very significant for the decision of surgical margins of tongue cancers. Doppler mode in US is a very useful modality in the differential diagnosis between normal and metastatic lymph nodes in patients with oral squamous cell carcinoma. FNA for mass-like lesions and OK-432 administration for ranulas also began as interventional radiology techniques using US in the oral and maxillofacial regions. Further investigation is needed to standardize the methods of US for diagnosing various kinds of diseases in the oral and maxillofacial regions. The clinical application of US in the oral and maxillofacial regions should be advocated in various publications.

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Research Article

Length and Geometric Patterns of the Greater Palatine Canal Observed in Cone Beam Computed Tomography

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The greater palatine canal is an important anatomical structure that is often utilized as a pathway for infiltration of local anesthesia to affect sensation and hemostasis. Increased awareness of the length and anatomic variation in the anatomy of this structure is important when performing surgical procedures in this area (e.g., placement of osseointegrated dental implants). We examined the anatomy of the greater palatine canal using data obtained from CBCT scans of 500 subjects. Both right and left canals were viewed ($N = 1000$) in coronal and sagittal planes, and their paths and lengths determined. The average length of the greater palatine canal was 29 mm (±3 mm), with a range from 22 to 40 mm. Coronally, the most common anatomic pattern consisted of the canal traveling inferior-laterally for a distance then directly inferior for the remainder (43.3%). In the sagittal view, the canal traveled most frequently at an anterior-inferior angle (92.9%).

1. Introduction

The anatomy of the greater palatine canal is of interest to dentists, oral maxillofacial surgeons, and otolaryngologists performing procedures in this area (e.g., administration of local anesthesia, dental implant placement, orthognathic Le Fort I osteotomies, and sinonasal surgeries) [1–6]. It houses the descending palatine artery (a branch of the third division of the maxillary artery) and greater and lesser palatine nerves (branches of the maxillary division of the trigeminal nerve) and their posterior inferior lateral nasal branches [2]. The trigeminal nerve provides sensory innervation to all of the maxillary and mandibular teeth and surrounding tissues. The trigeminal nerve splits into three branches in the middle cranial fossa, which exit through separate foramina. The maxillary division of the trigeminal (V2) exits the skull through the foramen rotundum where it transverses high in the pterygopalatine fossa. It enters the floor of the orbit and bone again anteriorly through the inferior orbital fissure in the posterior maxilla and travels towards the face. The maxillary division innervates all maxillary teeth, maxillary palatal and gingival tissue, skin of the midface, the nasal cavity, and sinuses [7]. The nerve of the pterygoid canal also enters the pterygopalatine fossa from the posterior, usually slightly inferior to the foramen rotundum, and transmits the nerve of the pterygoid canal. The greater palatine canal travels inferiorly from the pterygopalatine fossa, housing the greater palatine and lesser palatine nerves, which diverge to enter the hard palate at respective foramina [7].

Blocking sensation of the maxillary nerve in the pterygopalatine fossa by administering a maxillary division block achieves anesthesia to all of the above mentioned structures. A common technique to achieve a maxillary division block is the greater palatine canal approach in which a needle is inserted through the greater palatine foramen and advancing the needle until it is in the inferior portion of the pterygopalatine fossa, where anesthetic is deposited. Infiltration of local anesthetic into the greater palatine canal can also be employed to obtain vasoconstriction during endoscopic sinus surgery (ESS) [1]. In this procedure, the needle is advanced to the limit of the greater palatine canal, but not into the fossa, to avoid the potential complication of

arterial puncture [1]. Further advancement of the anesthetic syringe to reach the infraorbital nerve, located deep in the pterygopalatine fossa, is required when regional maxillary anesthesia is desired [1, 4, 5]. Therefore, knowing the anatomy and average lengths of the greater palatine canal is important when employing these techniques.

The walls of the greater palatine canal are formed anteriorly by the infratemporal surface of the maxilla, posteriorly by the pterygoid process of the sphenoid, and medially by the perpendicular plate of the palatine [7]. The maxillary sinus is located anterior, and the nasal cavity and concha medial and the pterygoid plates posterior to the greater palatine canal. The anatomy of these structures undoubtedly affects the anatomy of the greater palatine canal due to their proximal relationships. When performing surgical procedures in this area, preservation of the descending palatine artery and palatine nerves is essential to avoid excessive bleeding and to maintain nerve supply to the maxilla [8]. In other cases, regional nerve block may be unsuccessful if excessive resistance is met when injecting local anesthesia into the greater palatine canal, presumably the result of anatomic variation.

The purpose of this investigation was to determine the average length of the greater palatine canal and identify the most common anatomic pathways of this structure using cone beam computed tomography (CBCT) data obtained from patients at a dental school setting.

2. Methods

CBCT data obtained from 500 patient scans were reviewed. The CBCT scans were obtained between August 2005 and April 2007 at Creighton University School of Dentistry for a variety of dental indications. Scans were performed at 0.3 mm voxels. Canals were viewed and analyzed in both sagittal and coronal planes. Xoran technologies (Imaging Sciences International) i-CAT workstation program was used to visualize the data and to record canal path and length.

The length and anatomic paths traveled by both the right and left greater palatine canals ($N = 1000$) were determined. While both the foramen rotundum and pterygoid canal enter the pterygopalatine fossa from the posterior aspect, their locations are variable [9]. For this study, the pterygoid canal was selected as the superior limit instead of the foramen rotundum due to its ease of identification in relation to the greater palatine canal. Thus, the length of the greater palatine canal was defined as the bony portion of the greater palatine canal measured from the center of the pterygoid canal, as the center point of the pterygopalatine fossa, to the greater palatine foramen on the inferior surface of the hard palate. Soft tissue depth was not included. The pterygoid canal was marked in a superior-inferior direction with the use of the program's line coordinates so its vertical location was known while navigating through plane slices. The greater palatine canal was then measured from the marked vertical level to the apparent opening at the greater palatine foramen on the hard palate of both coronal and sagittal sections. In the sagittal plane, the inferior limit of the greater palatine canal was measured to the posterior wall of the great palatine foramen and in the coronal plane to the inferior surface of the horizontal hard palate for standardization due to variance in the foramen shape. Length of the canal was measured in millimeters using the Xoran software, following the most straight-line path through the center of the canal. The path of the greater palatine canal was recorded as the description of the descending length tracing lines in the canals. A compass was used on the CBCT images to record deviation from vertical. Length and path trends were analyzed for averages with standard deviations. The major anatomical landmarks are shown in Figure 1.

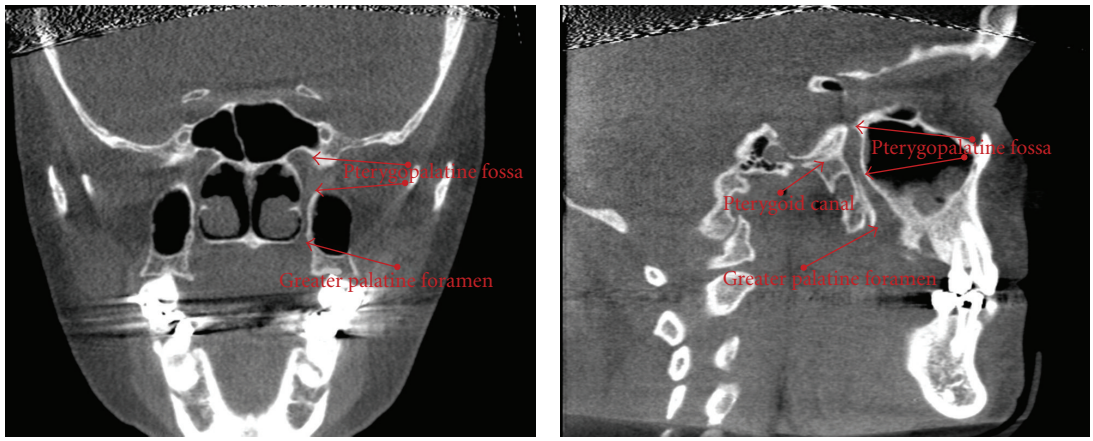
3. Results

Of the 500 subjects, 265 (53%) were female and 235 (47%) were male ranging in age from 18–73. The average length of the greater palatine canal was 29 mm (±3 mm), ranging from 22 to 40 mm.

The directional pathways observed in the coronal plane are summarized in Figure 2. Three pathways were consistently observed: (1) the greater palatine canal travels directly inferior from the pterygopalatine fossa (Figure 2(a)), (2) the greater palatine canal travels inferior-lateral for a distance then changes direction to pass directly inferior for the remainder of the canal (Figure 2(b)), and (3) the greater palatine canal travels inferior-lateral for a distance then changes direction to pass inferior-medial for the remainder of the canal (Figure 2(c)).

The directional pathways observed in the sagittal plane are summarized in Figure 3. In this plane, two pathways were observed: (1) the greater palatine canal travels in an anterior-inferior direction from the pterygopalatine fossa (Figure 3(a)) and (2) the greater palatine canal travels directly inferior for a distance and then changes direction to pass anterior-inferior for the remainder of the canal (Figure 3(b)).

The incidences of the directional pathways are summarized in Table 1 and the average angles and directional distances are summarized in Table 2. In the coronal plane, the most common pathway observed was the greater palatine canal traveling inferior-lateral for a distance then changing direction to pass directly inferior for the remainder of the canal (Figure 2(b)). This occurred in 43.3% of the total canals. In these cases, the average angle from the vertical was 28 (±6) degrees and occurred for 8 (±2) mm before traveling inferiorly. The next most frequent pathway was observed when the greater palatine canal traveled directly inferior from the pterygopalatine fossa (Figure 2(a)). This pathway occurred in 39.5% of the canals. The third pathway observed in the coronal plane was when the greater palatine canal traveled inferior-lateral for a distance then changed direction to pass inferior-medial for the remainder of the canal (Figure 2(c)). This occurred in 16% of the population. In these cases, the average angle from the vertical was 25 (±7) degrees and occurred for 10 (±3) mm before traveling medially at an average angle of 11 (±5) degrees from the vertical for the remainder of the canal.



(a) (b)

Figure 1: The images above demonstrate the appearance of anatomical structures on CBCT images described above; coronal view (a) and sagittal view (b). From the coronal view, the pterygopalatine fossa and greater palatine canal can be seen lateral to the nasal cavity. The pterygopalatine fossa begins below the middle cranial fossa and meets the greater palatine canal below which extends to enter the hard palate at the greater palatine foramen. In the sagittal view, the pterygopalatine fossa and greater palatine canal can be seen again, posterior to the maxillary sinus. The pterygoid canal is visible here, entering the pterygopalatine fossa from the posterior. The midpoint of the pterygoid canal was determined in this plane for each canal and used as the superior point of measurement.

Table 1: Incidence of pathways of greater palatine canal. The table below summarizes the frequency of canal pathways observed in both the medial-lateral and anterior-posterior planes, unilaterally (out of each 500 right and 500 left), bilateral symmetry (out of 500 pairs), and overall incidence (out of 1000 right and left canals).

Figure	Pathway	Right canal	Left canal	Bilaterally symmetrical	Overall incidence
	Medial-Lateral (Coronal) Direction				
Figure 2(a)	Canal travels directly inferior from fossa	45% (223)	34% (172)	22% (112)	39.5%
Figure 2(b)	Canal travels inferior-lateral for a distance then directly inferior for the remainder	39% (193)	48% (240)	23% (114)	43.3%
Figure 2(c)	Canal travels inferior-lateral for a distance then inferior-medial for the remainder	15% (77)	17% (83)	6% (31)	16%
	Other	1% (7)	1% (5)	0	1.2%
	Anterior-Posterior (Sagittal) Direction				
	Canal travels anterior-inferior	91% (456)	94.5% (473)	88% (441)	92.9%
Figure 3(a)	Canal travels directly inferior for a distance then anterior-inferior for the remainder	8% (40)	5% (25)	2% (10)	6.5%
Figure 3(b)	Other	1% (4)	0.5% (2)	0.02% (1)	.06%

In the sagittal plane, the most common pathway was the greater palatine canal travels in an anterior-inferior direction from the pterygopalatine fossa (Figure 3(a)), which was observed 92.9% and an average angle of 27 (±6) degrees. In 6.5% of the canals, the greater palatine canal traveled directly inferior for a distance and then changed direction to pass anterior-inferior for the remainder of the canal (Figure 3(b)). In these cases, after traveling directly inferior from the pterygopalatine fossa for 9 (±4) mm, the angle from the vertical was 33 (±6) degrees and occurred for 8 mm before traveling inferiorly.

4. Discussion

The use of the greater palatine canal as a route for injection of local anesthetic has many advantages. In studies by Wong and Sved [4] and Lepere [5], they note that the maxillary nerve

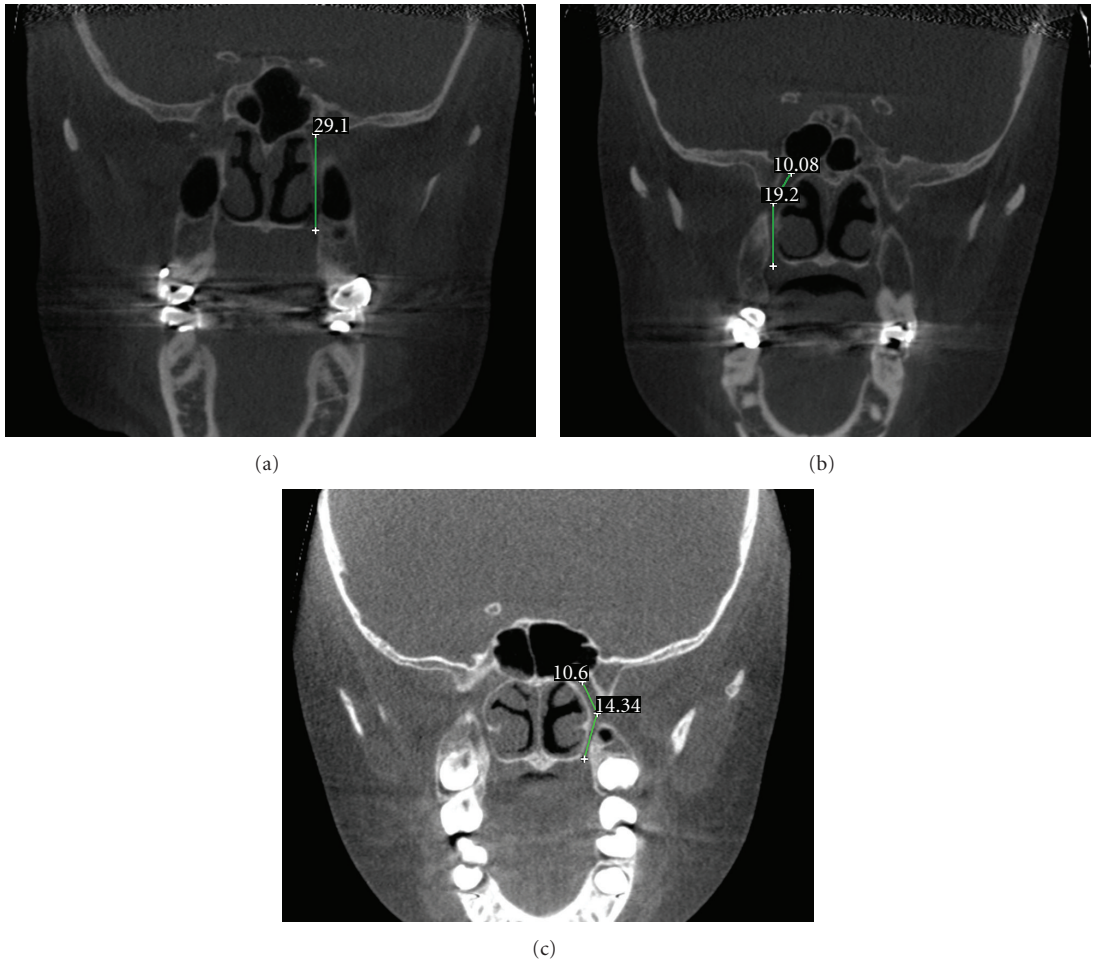
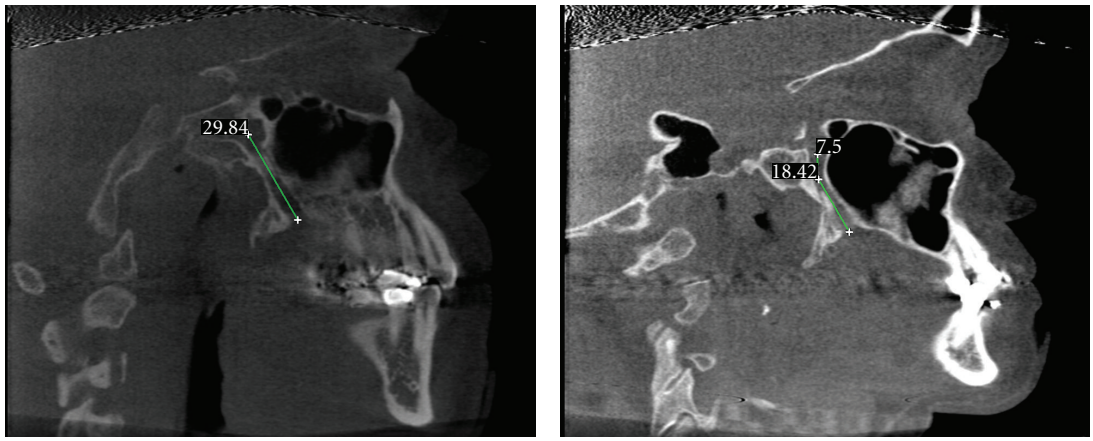


Figure 2: The coronal images above, showing unilaterally traced canals of three different subjects, were selected as examples of the most common canal pathways observed in the medial-lateral plane. The images also demonstrate how the canal paths and lengths were determined; the most straight-line path in the center of the canal, superiorly from the midpoint of the pterygoid canal entrance into the pterygopalatine fossa to the inferior surface of the horizontal hard palate. In some cases, bilateral canals could be traced in the same sagittal slice if both appeared patent (c), but in most cases only one patent canal was visible in a single slice and navigation anterior or posterior was required to see the other. Most common canal pathways demonstrated in the images are (a) canal travels directly inferior from fossa, (b) canal travels inferior-lateral for a distance then directly inferior for the remainder, and (c) canal travels inferior-lateral for a distance then inferior-medial for the remainder.

block would be advantageous for palatal surgery, periodontal surgery involving maxillary teeth, Caldwell-Luc procedure, quadrant restorative dentistry of the maxilla, multiple extractions, or a diagnostic aid due to local infection. Buddor summarizes use of the block in general anesthetics for awake intubation [10]. Additionally, it is indicated for hemostasis and anesthesia in endoscopic sinus surgery, septorhinoplasty, and posterior epistaxis [1, 11]. According to Wong and Sved [4], the absolute contraindication for use of the maxillary nerve block technique is when there is palatal swelling located around the greater palatine foramen. Like any maxillary nerve block, several complication are possible, including intravascular injection, nasal bleeding, diplopia, neural injury, anesthetic failure (due to incorrect angulation, insufficient needle penetration, inability to locate the greater palatine foramen, or intravascular injection), and insufficient anesthesia [3, 5, 12].

Since several of the procedures for which the palatine block may be indicated are generally of a more complex clinical nature (e.g., dental implant placement), it is not unreasonable that the clinician may have already have CBCT data obtained prior to the procedure. In this situation, the clinician may wish to analyze the anatomy of the greater palatine canals in a manner similar to that employed in this study to determine the potential likelihood of encountering complications. However, in the absence of such pretreatment CBCT data, a number of conclusions derived from this study are of benefit to the clinician. Previously, most data had been collected from human skulls. Malamed and Trieger thoroughly examined 204 skulls and observed that the optimal angle for needle penetration was 45.88 degrees and in over 97% of the skulls a probe could be passed from the greater palatine foramen into the pterygopalatine fossa without difficulty [6]. With CBCT we were able to



(a) (b)

Figure 3: The unilateral sagittal images above, from two different subjects, were selected as examples of the most common canal pathways in the anterior-posterior plane. Most common sagittal canal pathways as demonstrated in the images are (a) canal travels anterior-inferior and (b) canal travels directly inferior for a distance then anterior-inferior for the remainder.

Table 2: Average angles and directional distances of observed canal pathways. The table below summarizes the average angle and distance traveled in each component when a canal traveled of the vertical in each of the major canal pathways in both planes. The straight inferior trend viewed in the coronal plane is not included because canals following this pathway followed a direct vertical path.

Figure	Pathway	Directional distance	Right canal	Left canal
		Medial-Lateral (Coronal) Direction		
Figure 2(b)	Canal travels inferior-lateral for a distance then directly inferior for the remainder	Inferior-lateral angle (degrees)	28 (±6)	28 (±6)
		Inferior-lateral distance (mm)	8 (±2)	8 (±4)
Figure 2(c)	Canal travels inferior-lateral for a distance then inferior-medial for the remainder	Inferior-lateral angle (degrees)	25 (±7)	23 (±3)
		Inferior-lateral distance (mm)	10 (±3)	11 (±4)
		Inferior-medial angle (degrees)	11 (±5)	11 (±4)
		Anterior-Posterior (Sagittal) Direction		
Figure 3(a)	Canal travels anterior-inferior	Anterior-inferior angle (degrees)	27 (±6)	27 (±6)
Figure 3(b)	Canal travels directly inferior for a distance then anterior-inferior for the remainder	Directly inferior distance (mm)	9 (±4)	8 (±3)
		Anterior-inferior angle (degrees)	33 (±6)	33 (±6)

observe the exact pathway of the greater palatine canal. The anterior posterior path of the canal appeared to be relatively consistent, with 92.9% of canals traveling at a straight anterio-inferior angle. The medial lateral anatomy was more varied, with the most common anatomy being a straight inferior path (encountered 39.5%). However, depending on the variation in this pathway, the difficulty in passing a needle from the greater palatine foramen to the pterygopalatine fossa can be understood.

The recommended length of insertion of the anesthetic needle into the greater palatine canal has been suggested to be anywhere from 25 mm (for hemostasis in sinus surgery) to 32–39 mm (for maxillary anesthesia) [1, 4, 5, 13]. Unusually long canals could lead to lack of anesthesia. Conversely, unusually short canals could have a higher occurrence of complications if standard needle advancement lengths are utilized. Therefore, knowledge of the average lengths of the canal is beneficial. Several previous studies have examined the length of the palatine. A cadaveric study from Thailand found the combined length of the greater palatine canal and pterygopalatine fossa to be 29.7 ± 4.2 mm, including 6.7 ± 2.3 mm of soft tissue [3]. Computed tomography studies have shown the length of the greater palatine canal to range from 27 to 40 mm, depending on the definition of

the superior limit, excluding the soft tissue [13]. The results of this study fell within previously established averages and ranges.

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Review Article

A Review of the Nonsurgical Treatment of Oral Leukoplakia

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The aim of this paper was to assess the nonsurgical treatment of oral leukoplakia (OL). A medline search from 1983 to 2009 was conducted. The topical or systemic nonsurgical treatments or combination of both was reviewed. The primary outcomes of interest were clinical resolution, malignant transformation, follow-up, and recurrence of OL. Studies showed a rate higher than 50% of clinical resolution with photodynamic therapy, beta-carotene, lycopene, or vitamin A. Few studies reported rates of recurrence from 5 to 67% and of malignant transformation from 8 to 23%. There is a lack of randomized clinical trials that assess the effectiveness of nonsurgical treatment of OL. At this time, randomized controlled trials for nonsurgical treatment of OL demonstrate no evidence of effective treatment in preventing malignant transformation and recurrence. It reinforces that even after clinical resolution, OL should be regularly followed.

1. Introduction

Oral leukoplakia (OL) is a premalignant lesion described as "a predominant white lesion of the oral mucosa which cannot be defined as any other known lesion" [1]. According to Warnakulasuriya et al. [2], the new concept of OL shall acknowledge white lesions with questionable risk of being an OL, being excluded any other pathologies or known disorders which do not present potential malignant risk such as candidiasis, lupus erythematosus, lichen planus, hairy leukoplakia, frictional keratosis, nicotinic stomatitis, and leukoedema [3, 4].

OL's etiopathogenesis encompasses two broad categories, as follows: OL of unknown etiology or idiophatic and OL associated with tobacco use [3]. OL is more often found among older and elderly men, and its prevalence increases with age advancement. It has been estimated that less than 1% of the affected men are younger than 30 years old and that the prevalence increases to 8% in male patients older than 70 years old and to 2% in female patients of 70 years or more. OL's histopathologic aspects may vary from epithelium atrophy to hyperplasia, which can be associated with varying degrees of epithelial dysplasia [4, 5].

OL located on the floor of the mouth, soft palate, and tongue are considered as high-risk lesions, while, in other areas, they may be considered as of low malignancy risk [5, 6]. OL has an annual malignant transformation rate of 0.1% to 17% [7–10]. Some factors may contribute to increase the chance of the OL becoming malignant [4, 6, 11, 12]; these include the following.

(1) Gender: female patients tend to present a higher risk of developing the malignant form [11, 12].

(2) A long-time OL lesion: OL resistant to the treatments and what persist for long time may have worse prognosis than recent [12].

(3) OL in sites of high risk: lesions in the floor of mouth, ventrolateral tongue and soft palate have a high risk of malignant transformation [6, 12].

(4) OL among nonsmokers (idiopathic): nonsmokers with OL have an increased rate of malignant transformation in relation to OL in smokers [11, 12].

(5) Nonhomogenous OL-type: nonhomogenous OL lesions have a mixed color of white and red alterations, and an exophytic, papillary, or verrucous aspect; regardless of treatment, they exhibit a high recurrence rate and often eventually transformation to squamous cell carcinoma [4, 12].

(6) Epithelial dysplasia: OL with moderate and severe dysplastic lesions had a significantly higher risk of developing a squamous cell carcinoma than OL without epithelial dysplasia or with mild epithelial dysplasia [7, 9, 12].

In order to conduct treatment for OL, the degree of epithelial dysplasia may be assessed. In the presence of moderate or severe epithelial dysplasia, surgical treatment is recommended [9]. However, OL presenting low to moderate malignant risk may be either completely removed or not, and the decision should consider other factors such as location, size and, in the case of smokers, the patient's engagement in smoking cessation [4, 9, 13]. OL surgical treatment may be performed either through conventional surgery [4, 5, 14], electrocauterization, laser ablation [15, 16], or cryosurgery [17, 18]. Recurrence of OL after surgical treatment has been reported in 10%–35% of cases [19–22].

Nonsurgical treatment may also be considered for the management of OL [17, 18, 23]. This modality offers minimal adverse effects to patients, especially for patients with widespread OL that involves a large area of the oral mucosa or patients with medical problems and, consequently, high surgical risks [24]. Additionally, potential advantages of the nonsurgical treatment of OL include easy application that does not require treatment at a medical center and relative low cost [25].

The purpose of this paper is to present the current nonsurgical treatment options for OL. A Medline from 1983 to 2009 search was conducted using the following keywords: nonsurgical treatments of OL, retinoids, carotenoids, lycopene, photodynamic therapy. We included 21 studies of patients with diagnosis of OL. The primary outcomes of interest were clinical resolution, follow-up, and when reported, malignant transformation and recurrence. The topical or systemic nonsurgical treatments or combination of both were reviewed. Furthermore, the mechanisms of action, biodisponibility, toxicity, and side effects of these treatments were analyzed. Table 1 presents the nonsurgical treatment options for OL.

2. Carotenoids

2.1. Beta-Carotene. The carotenoids are a group of extremely hydrophobic molecules with little or no solubility in water [26]. Beta-carotene is a carotenoid commonly found in dark green, orange or yellowish vegetables, such as spinach, carrots, sweet potato, mango, papaya, and oranges [27]. Beta-carotene is a vitamin A precursor [26, 28–30]. The only known effect of excessive beta-carotene intake is a state in which the skin becomes strongly yellowish, the so-called carotenodermy, which disappears in a few weeks after the reduction of consumption [26]. While some authors have demonstrated the absence of side effects in patients that have received beta-carotene treatment [27], in other studies, the supplement diet based on beta-carotene caused headaches and muscle pain in some of the patients [31].

The use of beta-carotene has been recommended in order to prevent OL and possibly oral cancer [31]. The potential benefits and protective effects against cancer are possibly related to its antioxidizing action [32–34]. This function is accomplished through a ligation between beta-carotene and oxygen, which is an unstable reactive molecule, thus diminishing the damaging effects of free radicals [34, 35]. According to Liede et al. [32], a diet supplemented with beta-carotene can prevent changes in the oral mucosa, especially in smoker patients, who present low serum levels of vitamin C and beta-carotene when compared to nonsmokers. It has also been shown that beta-carotene has a better therapeutic clinic response in the prevention of OL lesions in smoker patients than in the nonsmoker ones [36]. Results from Sankaranarayanan et al. [31] demonstrated that one third of patients (15 out of 46) that used 360 mg beta-carotene per week during 12 months presented a complete resolution of OL. In the evaluative sessions one year after the treatment, 8 out of 15 (54%) of the patients who had a complete response presented recurrence. Moreover, 12 months after stopping the supplements, 5% (2 out of 15) of the patients who had made use of beta-carotene developed malignant neoplasia adjacent to the OL. Side effects were observed in 5 patients, being 3 with headaches and 2 developed muscular pain.

In another study, 23 patients with OL were treated with beta-carotene, in oral doses of 90 mg/day, for three cycles of 3 months each. Of 18 patients who completed the study, 6 (33.3%) showed complete clinical response. No significant clinical signs of toxicity were detected in any of the patients [37].

Twenty-four patients with OL were employed in another study with beta-carotene employed at a dose of 30 mg/day for six months. Only 2 patients (8.3%) presented a complete clinical response and 15 patients (62.5%) had partial clinical response [38]. Garewal et al. [39] evaluated 50 patients with OL, treated with beta-carotene at a dose of 60 mg/day, for six months. Only 2 patients (4%) demonstrated a complete clinical response. Relapses were found in 4 patients. A second biopsy was obtained after 6 months of therapy in 23 patients. There was no change in the degree of dysplasia in 14, with improvement of at least 1 grade in 9 (39%).

In the revised studies, the percentage of patients with clinical resolution ranged from 4% to 54%, with dosages regimes from 20 to 90 mg/day of beta-carotene in time periods from 3 to 12 months (Table 1).

2.2. Lycopene. Lycopene is a carotenoid without provitamin A action. This is a fat-soluble red pigment found in some fruit and vegetables. The greatest known source of licopene is tomatoes, which are widely employed in cooking [40]. There is a positive relationship between lycopene

Table 1: Nonsurgical treatments options for oral leukoplakia.

Author	Therapy	Dose	Number of patients	Clinical resolution (%)	Follow-up (months)	Recurrence	Malignant transformation (%)
Benner et al. [66]	Systemic Alfa tocoferol	400 IU	43	20%	24	NR	NR
Garewal et al. [38]	Systemic Beta-carotene	30 mg/day	24	8%	6	NR	8%
Toma et al. [37]	Systemic Beta-carotene	90 mg/day	23	26%	7	5%	NR
Sankaranarayanan et al. [31]	Systemic Beta-carotene	360 mg	46	54%	12	5%	NR
Liede et al. [32]	Systemic Beta-carotene	20 mg/day	24	NR	60–84	NR	NR
Garewal et al. [39]	Systemic Beta-carotene	60 mg/day	50	4%	18	17%	8%
Sankaranarayanan et al. [31]	Systemic Isotretinoin	300.000 IU	42	52%	12	67%	NR
Stich et al. [74]	Systemic Vitamin A	200.000–300.000 IU	21	57%	12	NR	NR
Nagao et al. [47]	Systemic Lycopene	NR	48	NR	NR	NR	NR
Singh et al. [48]	Systemic Lycopene	4–8 mg	58	25-55%	3	NR	NR
Hammersley et al. [24]	Topical Bleomycin	0,5%	8	NR	12	NR	NR
Epstein et al. [25]	Topical Bleomycin	1%	19	32%	40	NR	11%
Shah et al. [73]	Topical Vitamin A	1–5 mg	11	27%	11	18%	NR
Epstein and Gorsky [78]	Topical Tretinoin	0,05% gel	26	27%	42	40%	NR
Piattelli et al. [72]	Topical Isotretinoin	1%	10	10%	48	NR	NR
Lippman et al. [88]	Systemic 4 HPR	200 mg/day	35	0	9	NR	23%
Tradati et al. [87]	Topical 4 HPR	NR	8	25%	NR	NR	NR
Kübler et al. (1998)	Topical PDT	ALA 20%	20	25%	3	NR	NR
Siéron et al. [90]	Topical PDT	ALA 10%	5	80%	6	20%	NR
Sieroń et al. [96]	Topical PDT	ALA 10%	12	83%	6	8%	NR
Chen et al. [97]	Systemic PDT	ALA	24	33%	NR	NR	NR

IU: International Unit; NR: not reported; 4 HPR: Fenretinide; PDT: Photodynamic therapy; ALA: Aminolevulenic acid.

consumption and a reduction in the risk of the development of degenerative diseases caused by free radicals, such as cancer and cardiovascular diseases [41, 42]. Lycopene has the uncommon feature of becoming bound to chemical species that react to oxygen, thus being the most efficient biological antioxidizing agent [41]. Due this property, studies have been enthusiastically conducted with lycopene, in order to find out whether or not it could be an alternative to protect patients against the damaging effects of free radicals [41]. In addition to its antioxidizing property, lycopene also has the capacity to modify intercellular exchange junctions, and this is considered to be an anticancer mechanism [41]. In vitro experiments have shown the inhibition of the process of human neoplastic cellular growth by lycopene, since this protein interferes in growth factor receptor signaling and, thus, in cellular cycle progression, as previously demonstrated for neoplastic cells from the prostate gland [43].

Consumed carotenoids are incorporated in lipidic micelles and are absorbed by enteric mucosa through passive diffusion and distributed to the organs by the plasmatic lipoproteins. Lycopene release from the food matrix, presence of fat in the diet, and heat-induced isomerization from trans to cis mode are some factors influencing lycopene absortion and biodisponibility [44].

Lycopene is better absorbed in oil resin capsules and in tomato juice than in the form of raw tomatoes [45].

Hoppe et al. [46] determined the biodisponibility of one synthetic type of lycopene, in contrast with the performance of a lycopene oil resin extracted from tomatoes, and concluded that both sources of lycopene have the same bioavailability. Nagao et al. [47] evaluated 48 patients with OL (38 men and 10 women) and 192 control patients to verify the relationship between OL with serum levels of retinol, alpha-tocopherol, zeaxantine and luteine, cryptoxantine, lycopene, and alpha and beta-carotenes. The serum levels of lycopene and beta-carotene, among the 38 men suffering from OL, were significantly lower than those of the control group ($P < .005$). Authors suggested that improvement of micronutrient levels of beta-carotene and lycopene in Japanese males with a high frequency of smoking habit may protect against the relative risk of OL in this population.

Singh et al. [48] assessed the efficiency of lycopene in 58 cases of OL. The patients were divided into three groups, and received 8 mg/day, 4 mg/day, and placebo for a period of three months. The supplementation of lycopene (8 mg/day and 4 mg/day) reduced hyperkeratosis (clinically measured by the size of the lesion) with a similar efficiency in 80% of the cases. The complete clinical response of patients receiving 8 mg/day was 55% and 4 mg/day was 25%, but this difference was not statistically significant.

No systemic significant toxical effect of lycopene has been observed and there is no evidence of side effects from the treatment with lycopene [49]. Lycopene is a promising candidate in reducing cancer and chronic diseases in human beings; however, further research is needed to clarify its potential function in human health, according to the following criteria [50, 51].

(1) Factors influencing the uptake of lycopene in the diet, including the way it interacts with other carotenoids.

(2) Human metabolism and the possible function of the metabolites and cis-trans isomers.

(3) Mechanisms of the direct or indirect modulation of cancer.

(4) Studies based on evidences of treatment in human beings.

(5) Mechanisms of lycopene deposition in human tissues.

(6) Lycopene effects in the immunological system.

Only one study evaluated lycopene in clinical resolution of OL. The time period was three months, the dosages regimes from 4 mg/day and 8 mg/day and patients had clinical resolution 25 and 55%, respectively (Table 1).

3. Vitamins

3.1. L-Ascorbic Acid (Vitamin C). L-ascorbic acid (L-AA), the so-called vitamin C, is found in citrous fruits such as kiwi, strawberries, papaya, and mango [52]. The current US recommended daily allowance for ascorbic acid ranges between 100–120 mg/per day for adults [52]. It has been suggested that a daily intake of at least 140 mg/day is required for smokers because they usually present a reduction of the L-AA concentration in serum leukocytes [53].

L-AA has antioxidizing properties and reacts with superoxide produced as a result of the cells' normal metabolic processes; this inactivation of superoxide inhibits the formation of nitrosamines during protein digestion and helps avoid damage to DNA and cellular proteins [54]. L-AA toxicity does not occur, since vitamin is water-soluble and a decrease in absorption efficiency occurs when consumption exceeds 180 mg/day [55].

The ability of L-AA to maintain oral mucosa integrity is very little documented. One study examined the presence of oral mucosal lesions in subjects with low L-AA levels in plasma, compared to controls. Subjects with low plasma L-AA levels $\leq 25\,\mu$mol/l) ($n = 106$) formed the study group and individuals with normal L-AA levels ($\geq 50\,\mu$mol/l) ($n = 103$) formed the control group. Oral mucosal lesions in all subjects were defined clinically as petechias, OL, and lichenoid lesions. There was a statistically significant difference between the groups only for OL, where the prevalence of OL was higher when smoking was combined with L-AA deficiency [56].

In another study [57], 24 OL patients were treated with an association of beta-carotene, vitamin E, and L-AA, and an increase was observed in the reversion of oral mucosa dysplasia. In 97.5% of patients, dysplasias were diminshed by use of antioxidant combinations. The reversion of the oral mucosa dysplastic changes was more evident in the patients using antioxidative vitamins that stopped smoking and ingestion of alcohol.

There are no studies regarding the efficacy of the use of L-AA alone for OL treatment.

3.2. α-Tocoferol (Vitamin E). α-Tocoferol (AT) is the commonest and most active form of vitamin E. It is found in plant oil, margarine, and green leaves [58–61]. The recommended daily limit rates are 10 mg/day for adult men and 8 mg/day for adult women [62]. Its absorption rate is reduced when consumption exceeds 30 mg/day [63]. α-Tocoferol is an effective antioxidant at high levels of oxygen, protecting cellular membranes from lipidic peroxidation [59, 60, 64, 65]. Erhardt et al. [35] showed that supplementation with AT led to a significant rise in the concentration of this antioxidant in the plasma. In contrast, supplementation did not lead to a significant increase in the concentration of AT in cells of the oral mucous membrane.

Benner et al. [66] evaluated the toxicity and efficacy of AT in 43 patients with OL in use of 400 IU twice daily for 24 weeks. Follow-up was performed at 6, 12, and 24 weeks after the beginning of treatment to assess toxicity, clinical response, and serum AT levels. It was observed that 10 patients (23%) had complete clinical remission of lesion and 10 (23%) had a partial clinical response. Nine (21%) had histologic responses (complete reversal of dysplasia to normal epithelium). Mean serum AT levels were 16.1 μg/mL at baseline and increased to 34.29 μg/mL after 24 weeks of treatment.

Seventy-nine patients with OL were enrolled in an antioxidant supplementation program that consisted of 30 mg of beta-carotene, 1000 mg of L-AA, and 800 IU of AT per day, which were taken for 9 months. No side effects were noticed during the course of the study. Although no patients showed complete resolution of the OL, 55.7% showed reduction in the size of the OL after 9 months. Clinical improvement was observed in 90% of the patients who had reduced risk factors, compared with 48.8% of improvement in those who did not. Squamous cell carcinoma developed in seven patients (8.9%) within the preexisting OL during or shortly after completion of the study [33].

Some studies evaluated the administration of AT, alone or combined, used the dosage of 800 IU/day from 6 to 9 months (Table 1).

3.3. Retinoic Acid (Vitamin A). The current definition of retinoid includes all the natural and synthetic compounds with an activity similar to that of Vitamin A. Vitamin A exists in the human body as various interconvertible compounds, notably retinal (essential for vision) and retinol, which is the most potent analogue and the main form of storage and transportation [27, 67]. Retinoic acid is obtained from carotene and animal products such as meat, milk, and eggs, which, while in the intestine, are converted, respectively, into retinal and retinol [27, 67]. The absorption of retinoids increases by up to 50% when ingested with food. Retinoids are transported in the blood by plasmatic proteins. Hepatic metabolization is achieved via the action of cytochrome P-450 [27, 67]. Hypervitaminosis occurs when consumption exceeds the liver's capacity to store retinoids [30].

Topic retinoids were initially tested against diseases related to keratinization. 13-cRA was used for the first time against acne, in 1969. The so-called "retinoic dermatitis" is the main side effect of tretinoin, this leads to cutaneous irritation characterized by erythema, scaling, ardency, and/or pruritus. "Retinoic dermatitis" occurs frequently, and patients ought to be previously instructed with regard to its occurrence. Furthermore, patients should also be warned to avoid the sunlight and to wear sunscreen [68].

The use of systemic retinoids is not indicated in cases of (1) pregnancy or probability of pregnancy; (2) noncompliance with the use of contraceptives; (3) breast feeding; (4) hypersensitivity to parabeno (in isotretinoin capsules). It is, relatively, not indicated in cases of (1) leukopenia; (2) hypothyroidism (patients using bexarotene); (3) high levels of cholesterol and triglyceride; (4) hepatic malfunction; (5) renal malfunction [67, 69]. Absorption of systemic retinoids is boosted by up to 60% when they are taken together with the meals.

Supplementation with retinoids for OL treatment began in the 1960s. However, this treatment was not widely accepted due to its side effects—hypervitaminosis, toxicity, teratogenic effects, and alterations in various organic systems [70]. At the cellular-level, retinoids interact with surface receptors and penetrate the cell. They are subsequently metabolized and transported to the nucleus by various proteins. Retinoids affect diverse processes, such as keratin production, the expression of growth factors and kinases, oncogenesis, apoptosis, production of the collagen matrix, immunologic and inflammatory response, cellular differentiation, embrionary morphogenesis and carcinogenesis [26, 30].

13-cRA is the retinoid recommended for OL treatment. The use of 13-cRA has been shown to be effective in resolving OL [33, 34]. However, the high recurrence rates after short periods of discontinuance, together with its side effects, are limiting factors [33, 34, 70]. Various studies have evaluated the therapeutic effectiveness of vitamin A derivatives in the treatment of OL, although not all studies have shown concordant results (Table 1). In one study, of the 45 patients registered, 7 (15.5%) had OL. Patients received a fixed dose of 13-cRA (10 mg/day) plus an escalating dose (beginning at 800 IU/day, until 2000 IU/day) for 4 months. Seventy-one percent of OL patients had complete clinical responses [71]. A study conducted with retinoic supplementation (300.000 IU retinol acetate) for OL treatment demonstrated complete resolution in 52% of patients. Side effects observed included six patients with headaches, five patients reported muscle pain, and two patients reported dry mouth [31].

Kaugars et al. [34] implemented retinoic supplementation in various dosages for OL treatment. Fifty percent of patients had complete or partial clinical resolution of OL, but with side effects such as dizziness and headache. Moreover, for most of the patients with clinical resolution of the lesion, OL recurred upon the discontinuance of medication. Some patients ceased treatment due to its side-effects. On the other hand, during the assessment of 13-cRA topical use (0.1% isotretinoin gel) for 4 months, in 9 patients with OL, 20% showed complete clinical response to treatment and no patient reported adverse effects [72].

In another study, 13-cRA was used in 16 patients with OL for six months. Three patients were entered at a dosage of 3 mg/day, eight at 5 mg/day, and five at 10 mg/day. Eleven patients completed the study: 3 had complete clinical responses (2 at 10 mg/day and 1 at 5 mg/day). Recurrence was observed in two of these three patients [73].

During another study, patients with OL were distributed into two groups: one receiving 200.000 IU vitamin A per week ($n = 21$) and the other receiving placebo capsules ($n = 33$) for six months. Complete remission was observed in 57% of patients that received vitamin A. The administered doses of vitamin A did not produce any detectable adverse effects during the trial period. In the placebo group, 7 patients (21%) formed new OL; whereas no new OL developed in the vitamin A group over the 6 months [74]. In an additional study from these same authors, patients with OL were divided into three groups receiving: group 1, beta-carotene (180 mg/week); group 2, beta-carotene (180 mg/week) plus vitamin A (100.000 IU/week), and group 3 placebo, for 6 months. Remission of OL in group 1 (14.8%) and group 2 (27.5%) differed significantly from that seen in group 3 (3%). During the trial period, all patients continued to chew tobacco-containing betel quids [75].

In a study by Toma et al. [76], sixteen patients with OL were treated with oral 13-cis-retinoic acid. The initial dose, given for 3 months, was 0.2 mg/kg/day, increasing by

a further 0.2 mg/kg/day in successive 3 month cycles. The maximum dosage reached 1.0 mg/kg/day. Fourteen of the patients completed the trial and there was one complete response obtained at 0.4 mg/kg/day. After the retinoic acid treatment was stopped, patients were followed-up for 12 months; 2 patients showed regression of the responses obtained after 6 and 9 months [76].

One study, in two phases, was made in 70 patients with OL. In the first phase, the 67 patients were treated at a high dose of isotretinoin (1.5 mg/kg/day) for three months. Fifty-five percent of patients demonstrated complete or partial clinical responses. In the second phase of the study, 59 patients, with responses or stable lesions, were randomly assigned to maintenance therapy with either beta-carotene (30 mg/day; $n = 33$) or a low dose of isotretinoin (0.5 mg/kg/day; $n = 26$) for nine months. Twenty-two patients (92%) with isotretinoin and 13 patients (45%) with beta-carotene demonstrated a positive response [77].

Studies focusing on topical vitamin A and their derivates in the management of patients with OL have been reviewed by Gorsky and Epstein [23]. The use of topical tretinoin at 0.05% was evaluated in 26 patients with OL. Patients were followed for a mean of 23 months. Ten patients who had partial or no clinical response were submited at biopsies pre- and posttreatment, and the mean grade of histological features did not change. Twenty-seven percent of the patients had a complete clinical remission. Recurrence of OL was observed in approximately 40% of these patients after cessation of the applications. The use of topical vitamin A acid showed a limited effect in controlling OL [78].

In an open trial, the clinical efficacy of topical calcipotriol (vitamin D3 analogue) was compared with tretinoin in the therapy of hyperkeratotic oral lesions (leukoplakia). Forty patients had histologically proven OL, 20 were treated with calcipotriol (50 mg/g), and the other 20 with tretinoin cream (0.05%). The treatment was given for 5 weeks and follow-up was at 4 months, with clinical assessments at 2, 4, and 5 weeks. Results showed complete resolution of OL in 16 patients in both calcipotriol and tretinoin groups. No documented topical or systemic adverse reactions and results were maintained at 4 months [79].

In a 10-year study that followed OL patients, Scardina et al. [80] assessed the effectiveness of topical use of isotretinoin at 0.18%, as compared with 0.05%. Concentrations of 0.18% and 0.05% were given to two different groups and administered twice a day during 3 months. The clinical resolution was 85% in the 0.18% group, without any adverse topic or systemic reaction. In addition, epithelial dysplasia disappeared and there was a significant reduction in the size of the lesion.

In the systemic use with dosage of 300.000 IU of retinoic acid (Vitamin A), a clinical resolution of the 50% has been demonstrated. In topical use with dosage range from 0.05% to 1% a clinical resolution from 10% to 27% has been obtained (Table 1).

3.4. Fenretinide. Fenretinide (4-HPR) or N-(4-hydroxyphenyl) retinamide is a vitamin A analogue that was synthesized in the United States during the late 1960s. This retinoid shows a preferential accumulation in breast instead of liver [81], is effective in the inhibition of chemically induced mammary carcinoma in rats [82], and has proven to be less toxic than many other vitamin A analogues [82, 83]. A characteristic feature of 4-HPR is its ability to inhibit cell growth through the induction of apoptosis with mechanisms that may be both receptor-dependent and receptor-independent. Chemopreventive efficacy of fenretinide has been investigated in clinical trials targeted at different organs [84–86]. Eight patients with diffuse (nonoperable) oral lichen or OL were treated with 4-HPR applied topically twice daily. After one month of therapy, two patients had complete remission and the other six had a greater than 75% response. 4-HPR was well tolerated, and no local or distant side effects were observed [87].

A phase II trial of 4-HPR (200 mg/day) was carried out for 3 months in OL patients who had not responded ("de novo" resistance) or who had responded and then relapsed (acquired resistance) to the previous treatment with natural retinoids. Of 35 patients with retinoid-resistant OL, no patient had complete responses and 12 (34.3%) had partial responses to 4-HPR. Nine patients had clinical responses within 9 months of stopping 4-HPR. Toxicity was minimal and compliance was excellent [88].

Systemic use of 4-HPR with 200 mg/day for 3 months in 35 patients demonstrated partial clinical resolution of OL of 12 patients (Table 1).

4. Bleomycin

Bleomycin, a cytotoxic antibiotic, was first used for the treatment of neoplasms of the penis and scrotum, but has also been employed for squamous cell carcinoma of the head and neck region, oesophagus, and skin [89]. The most commonly adverse effects are mucocutaneous reactions, which include stomatitis, alopecia, pruritic erythema, and vesiculation of the skin [27]. Eight patients with OL were treated by the daily application of a 0.5% (w/v) solution of bleomycin sulphate in dimethyl sulphoxide (DMSO). After 12 to 15 applications, the white patch peeled off and the resultant raw suface was epithelialized over the following 14 days. Repeated biopsies showed a significant reduction of dysplasia and keratinisation [27]. The use of topical 1% bleomycin in DMSO was evaluated for the treatment of dysplastic OL. Bleomycin was applied once daily for 14 consecutive days to lesions of the oral mucosa in 19 patients. It was well tolerated with minor mucosal reactions. Immediate posttreatment biopsies showed that 75% of patients had resolution of dysplasia. Ninety-four percent of the patients attained at least partial clinical resolution. After a mean follow-up period of 3.4 years, 31.6% of patients had no clinically visible lesions. In 2 patients (11%), malignant transformation occurred [28].

Topical bleomycin in treatment of OL was used in dosages of 0.5%/day for 12 to 15 days or 1%/day for 14 days (Table 1).

5. Photodynamic Therapy

Photodynamic therapy (PDT) is a noninvasive method for the treatment of premalignant lesions and head and neck cancers [90, 91]. The principle of PDT is a nonthermal photochemical reaction, which requires the simultaneous presence of a photosensitising drug (photosensitiser), oxygen, and visible light. After a period to allow the photosensitiser to collect in the target tissue, the photosensitiser is activated by exposure to low-power visible light of a drug-specific wavelength. Mainly, the light source consists of a portable diode laser and the light is transmitted via laser fibres to or into the tumour. Illumination of the tumour by light at the activating wavelength results in the destruction of cells by a nonfree radical oxidative process. These reactive oxygen species may damage crucial cell components, such as structural proteins, enzymes, DNA, and phospholipids. PDT is a cold photochemical reaction, and the photosensitising agents are of inherently low systemic toxicity. PDT damage heals mainly by regeneration rather than scarring. Due to the organ preserving principle of PDT, important structures are maintained with good functional and cosmetic outcome [91, 92].

Several photosensitisers have been developed during the past. Haematoporphyrin and haematoporphyrin derivatives were the first photosensitisers. Four photosensitisers have been approved so far: (1) photofrin has been approved in many countries for the treatment of oesophagus cancer and lung cancer; (2) 5-Aminolaevulinic acid (ALA) was also approved in several countries for the treatment of skin cancer; (3) verteporfin for the treatment of macular degeneration (4) foscan is the only photosensitiser that has been approved for the treatment of advanced squamous cell carcinoma of the head and neck in Europe in the year 2001 [93].

The ALA is a naturally occurring compound in the haem biosynthetic pathway, which is metabolised to a photosensitive product, protoporphyrin IX (PpIX). The major advantage of ALA when compared to synthetic photosensitisers is the rapid metabolism, which significantly reduces the period of cutaneous photosensitivity [93]. For most indications in head and neck surgery, the photosensitiser is administered systemically by intravenous injection. Only for very superficial skin lesions or premalignant lesions of the oral mucosa, the ALA can be applied topically. For all other indications intravenous application is mandatory [93].

Zakrzewska et al. [94] reported three forms of treatment of 10 cases of proliferative verrucous leukoplakia; surgery, carbon dioxide laser; PDT. PDT was administered to 5 patients, in which there was no recurrence in 3, although a white halo of hyperqueratosis was observed around the area subjected to treatment. Results showed a recurrence rate, after treatment, of 100% for surgical excision and 85.7% for laser vaporization. PDT offered the best prognosis compared to the other forms of treatment. Kübler et al. [95] treated 20 patients with OL using PDT topic 20% ALA, followed by light jet at 630 nm, 100 W/cm2 and 100 J/cm2. After 3 months, 5 patients completely responded to the treatment (there were no clinical signs of OL), 4 partially responded (the lesion was reduced or looked better), 3 did not respond (no clinical change), and 1 had a partial response being submitted to treatment again, resulting in the disappearance of the lesion. No recurrence was observed at 9 months after this treatment.

Siéron et al. [90] treated 5 patients with OL using topical 10% ALA on the lesion, followed by argon laser (635 nm, 100–250 J/cm2). Four of the 5 patients completely responded. In one case, there was recurrence after 6 months, however, after 2 additional sessions, the lesions completely disappeared. This same author [96] observed the therapeutic response with PDT for OL in twelve patients topically treated with ALA at 10%, activated by a laser at 635 nm and 100 J/cm2 per session, for 6 to 8 sessions. There was a complete response (total wash out of the leukoplakia in the visual inspection confirmed by specimen biopsy) in 10 cases (83%). One recurrence was reported after 6 months of follow-up.

Chen et al. [97] treated 24 patients with OL using 20% ALA-PDT, once a week; another 24 patients used 20% ALA-PDT twice a week. In the latter group, 8 completely responded to the treatment, 16 partially responded, and 9 did not. All patients from the twice-a-week group responded significantly better than those treated only once a week.

From the studies using PDT-ALA in topical concentrations from 10 to 20%, it may be observed a clinical resolution of OL of the 25% to 80% (Table 1).

6. Conclusion

Several clinical trials have investigated the treatment of OL with use of supplements. Although the administration of retinoic acid and beta-carotene has some efficacy to resolve OL, the studies were based on small samples and short periods of follow-up. Given the side effects and counterindications of antioxidizing agents, with the exception of lycopene, the use of agents requires careful control. The small number of patients, the lack of controls, the lack of widely accepted criteria for classifying OL, the variability in nonsurgical treatment protocols, and differences in histopathologic evaluation difficult the interpretation of data of the few randomized clinical trials in nonsurgical treatment of OL. At this time, randomized controlled trials for nonsurgical treatment of OL demonstrate no evidence of effective treatment in preventing malignant transformation and recurrence. It reinforces that after clinical resolution, OL should be regularly followed.

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Case Report

Stafne's Defect with Buccal Cortical Expansion: A Case Report

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A rare case of Stafne's bone cavity, type III-G, is reported in a 49-year-old male patient who had been referred to a private clinic for a routine evaluation. The final diagnosis was based on computed tomography. Scintigraphy played a fundamental role in determining the most likely etiology.

1. Introduction

Stafne [1] first described lingual bone cavities near the mandibular angle and, based on data collected from his 34 patients (35 bone cavities), established that this condition involves mainly male patients between 40 and 50 years of age, is evenly distributed on both sides, and does not cause symptoms. The shape of a lingual bone cavity can be round or oval, and it varies from 1 to 3 cm in diameter. When the cavity is oval, the major axis is parallel to the mandibular border, and if it is wider than 3 cm, there may be interference in the continuity of the mandibular border, which can be felt by means of palpation. Stafne's bone defects (SBDs) occur below the mandibular canal, in an anterior position in relation to the angle of the mandible, at the level of the third molar. Radiographically, the cortical outline of the bone defect is denser and thicker than that of odontogenic cysts. Five of the 35 bone cavities were followed up over a period of more than 11 years and no change in size was noted.

Using computed tomography (CT) images, Ariji et al. [2] classified SBDs according to the depth and content of the cavities. According to depth, the bone defects were classified as follows.

(i) *Type I*: Cavity depth is limited to the medullar portion of the mandible.

(ii) *Type II*: Cavity depth reaches the buccal cortex of the mandible but does not cause its expansion.

(iii) *Type III*: Cavity depth reaches the buccal cortex of the mandible and causes its expansion.

According to content, they were classified as follows.

(i) *Type F*: Cavity is filled with fat.

(ii) *Type S*: Cavity is filled with soft tissue (lymphonode, vessel, conjunctive tissue, etc.).

(iii) *Type G*: Cavity is filled with part of the submandibular gland.

The aim of this work is to report on the rarest occurrence of this type of bone defect: SBD type III-G.

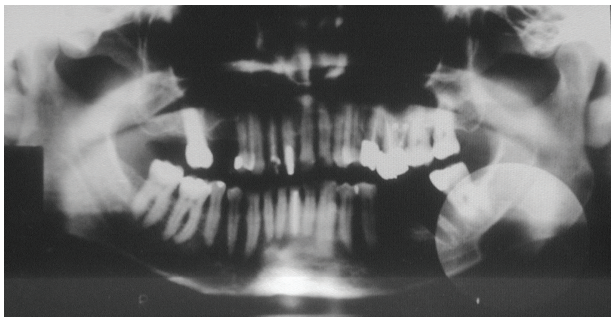

Figure 1: Panoramic radiography showing the radiolucent area.

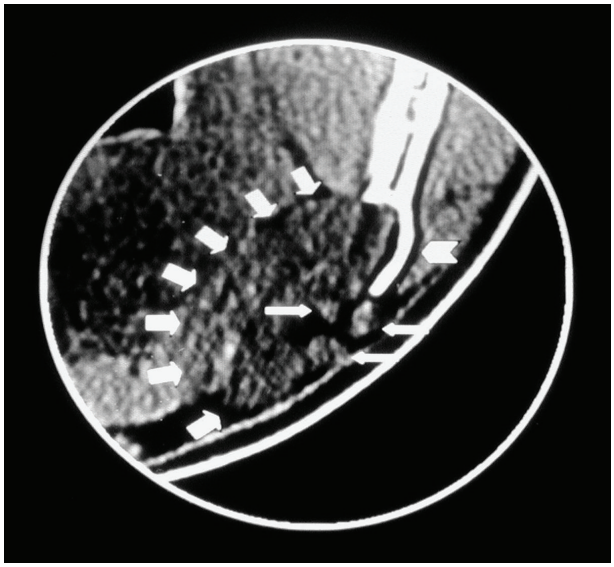

Figure 2: CT image:soft-tissue window and coronal view, in which the expansion of the mandibular buccal cortex (arrow head), the submandibular gland (large arrows), and some lymph nodes (small arrows) can be seen.

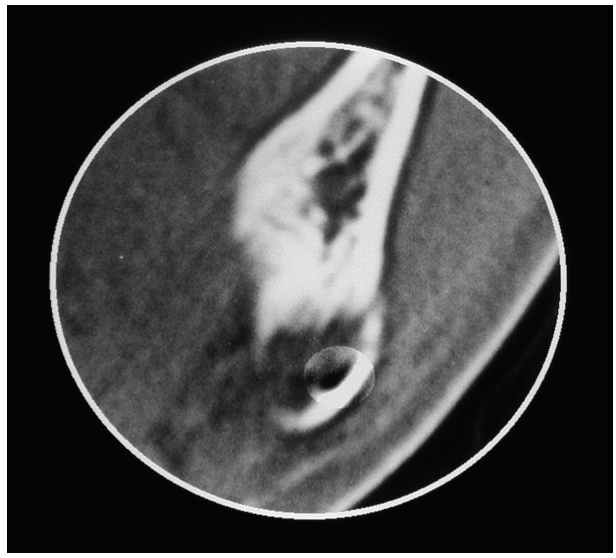

Figure 3: CT image:bone window and coronal view, in which the buccal location of the mandibular canal can be seen.

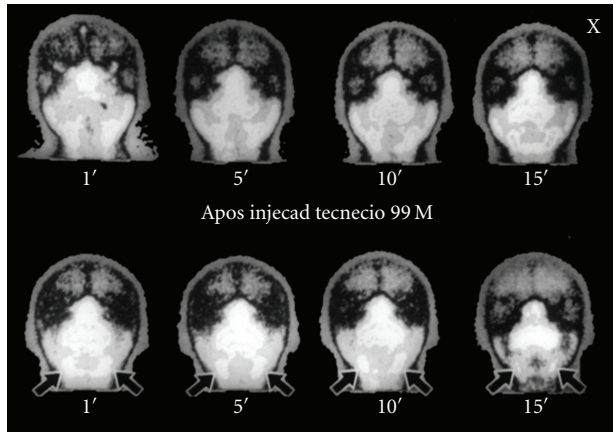

Figure 4: Scintigraphy revealing hyperretention of the radionuclide.

2. Case Report

A 49-year-old asymptomatic male patient was referred to a private clinic in order to undergo routine panoramic radiography. Results showed an oval-shaped, radiolucent area of cystic aspect and regular, well-defined cortical outline; its longest axis was placed horizontally in the left hemimandible. This lithic area, located under the lower left third molar, was anterior to the mandibular angle, and reached the border of the mandible, which showed thinner than normal width due to the presence of the bone defect. The apparent unity of the upper contour of the lesion and the upper wall of the mandibular canal gave them a thicker than normal appearance. The fact that the lower wall of the mandibular canal was visible within the radiolucent area showed that there could be a neighboring relationship, but not an involvement, of the inferior alveolar nerve (Figure 1).

As a hard buccal protuberance was perceived on palpation, a CT was performed. The coronal view in the CT scan showed that there had been a distention of the mandibular buccal cortex and that glandular tissue had been spreading into the bone defect. A further coronal view revealed the buccal location of the mandibular canal, which was preserved (Figures 2 and 3).

A previous scintigraphy revealed an inflammatory condition associated with an obstructive process involving the submandibular glands, particularly on the left side (Figure 4).

3. Discussion

The etiology of SBD was suggested by Stafne [1] to arise as early as the fetal period by failure of normal deposition of bone to fill the cavity formed by regressive changes of the lowest portion of condylar cartilage. Choukas and Toto [3] did not rule out a congenital origin, but advocated that entrapment of the superior lobe of the submandibular gland during mandible development would determine the

bone defect formation. They speculated that SBD may be the result of an erosive process caused by the superior lobe of the hypertrophic gland. A bone defect formation was documented by Tolman and Stafne [4] confirming that SBD may also have a developmental origin.

Recently, an extensive literature review [5] affirmed that all SBD variants (anterior:related to the sublingual gland, posterior:related to the submandibular gland, and of the ascending ramus:related to the parotid gland) are the result of an erosive process caused by pressure of hypertrophic/hyperplastic submandibular glands on the bone surface. However, the area of medial pterygoid muscle attachment was included as a site of SBD (posterior variant) presentation in Philipsen et al.'s study [5], where contact between the gland and mandible surface is improbable.

Minowa et al. [6] did not consider it reasonable that the gland exerts pressure and cavitation on the medial aspect of the mandible and speculated that SBD may have its origin in a benign lipoma or be the result of bone resorption due to an acquired vascular lesion. In addition, they refute the embryologic and congenital origin since SBD does not occur in children under 10 years of age.

In a report on a mandibular ramus-related Stafne's bone cavity [7], Campos et al. showed that there was no contact between the parotid gland and the bone surface at the site. Therefore, SBD may also be the result of a focal failure during intramembranous ossification of the mandible [7].

More recently, Shimizu et al. [8] refuted the vascular origin; SBD was assumed to be a gland-related condition, and dislocation of the submandibular gland was proposed as the cause of its occurrence.

This particular case clearly shows the relationship between the cavity and its corresponding submandibular gland. Due to a chronic inflammatory process detected in the scintigraphy, the gland seems hypertrophied and capable of exerting enough pressure to cause bone resorption. Moreover, we consider this pressure sufficient to cause distension of the buccal cortex. Thus, we agree with Campos [9] when he says that (1) submandibular gland hyperplasia/hypertrophy is the chief etiologic factor for the vast majority of cases of SBD, posterior variant, in the area free from medial pterygoid muscle attachment (2) a few cases of SBD, posterior variant, mostly in the area of medial pterygoid muscle attachment, are defects of embryologic origin and (3) vascular alterations have a contributory but not the main role in SBD formation.

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Research Article

Associations between the Cervical Vertebral Column and Craniofacial Morphology

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Aim. To summarize recent studies on morphological deviations of the cervical vertebral column and associations with craniofacial morphology and head posture in nonsyndromic patients and in patients with obstructive sleep apnoea (OSA). *Design*. In these recent studies, visual assessment of the cervical vertebral column and cephalometric analysis of the craniofacial skeleton were performed on profile radiographs of subjects with neutral occlusion, patients with severe skeletal malocclusions and patients with OSA. Material from human triploid foetuses and mouse embryos was analysed histologically. *Results*. Recent studies have documented associations between fusion of the cervical vertebral column and craniofacial morphology, including head posture in patients with severe skeletal malocclusions. Histological studies on prenatal material supported these findings. *Conclusion*. It is suggested that fusion of the cervical vertebral column is associated with development and function of the craniofacial morphology. This finding is expected to have importance for diagnostics and elucidation of aetiology and thereby for optimal treatment.

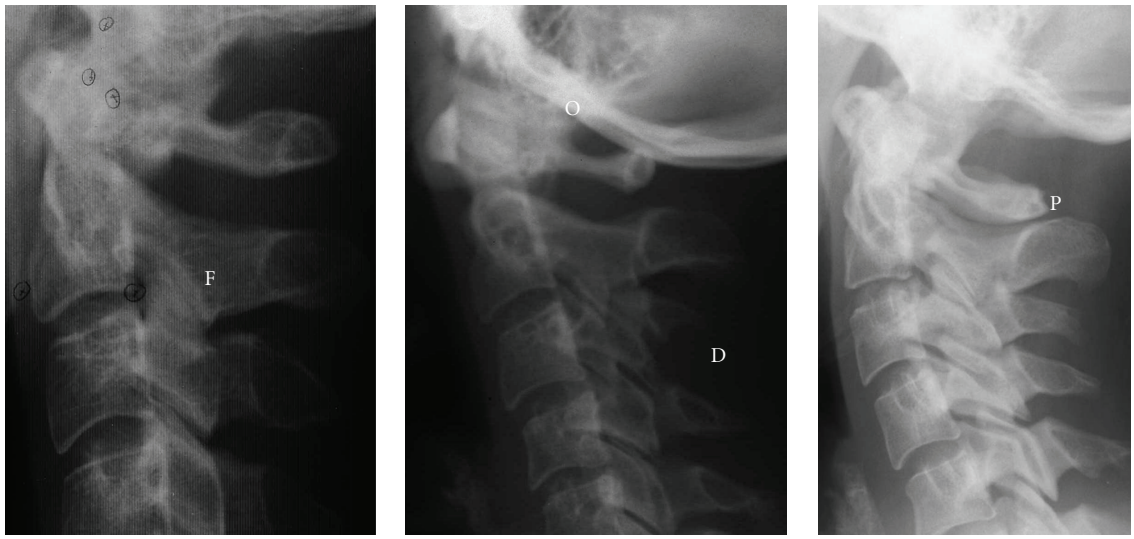
1. Introduction

Cephalometric analyses of the cervical vertebral column area have previously been performed on profile radiographs. It was found that the horizontal and vertical dimensions of the first cervical vertebra (C1), atlas, were associated with head posture, cranial base angulation, and mandibular shape and growth [1–4]. Also, posture of the head and neck was associated with factors such as craniofacial morphology including the cranial base [5–11], upper airway space [9, 12, 13], to some extent occlusion [14, 15], and temporomandibular disorders [16–21]. Many cross-sectional studies agree on a relationship between extended head posture and craniofacial structures [1, 5–10]. In subjects with extended head posture, increased anterior facial height, reduced sagittal jaw dimensions, and a steeper inclination of the mandible were generally observed. When the head was bent in relation to the cervical column, a shorter anterior facial height, larger sagittal jaw dimensions, and a less steep inclination of the mandible were observed. Some longitudinal studies likewise demonstrated that growth changes in head posture were related to corresponding changes in the growth pattern of the facial skeleton [22, 23]. When the head was extended, a reduced forward rotation of the mandible was observed.

Cephalometric studies of the cervical vertebral column area have also been performed on patients with obstructive sleep apnoea. Most of these studies agree that patients with obstructive sleep apnoea have an extended head posture [12, 24–31].

Until recently, deviations of the cervical vertebral column have only been described in relation to craniofacial syndromes and cleft lip and palate. Craniosynostosis syndromes, for example, Pfeiffer's, Crouzon's, and Apert's syndromes, showed deviations such as fusion anomalies [32–36]. Furthermore, deviations of the cervical column morphology were seen in Saethre-Chotzen, Klippel-Feil, Turner, and Down syndromes [37–41]. Also, malformations of the upper cervical vertebrae have been closely investigated in patients with cleft lip and/or palate [42–47].

Accordingly, associations have been reported between head posture and craniofacial morphology, between head posture and OSA, and between morphological deviations



(a) (b) (c)

Figure 1: Illustrations of morphological deviations of the upper cervical vertebral column. F: Fusion is defined as fusion of one unit with another at the articulation facets, neural arch, or transverse processes. O: Occipitalization is defined as assimilation, either partially or completely, of the atlas (C1) with the occipital bone. P: Partial cleft is defined as failure to fuse of the posterior part of the neural arch. D: Dehiscence is defined as failure to develop of part of a vertebral unit.

of the cervical vertebral column and craniofacial syndromes [32–36, 42–47] and cleft lip and/or palate. The aim of the present study was to summarize recent studies on morphological deviations of the cervical vertebral column and the associations with the craniofacial skeleton and head posture in nonsyndromic patients and in patients with obstructive sleep apnoea and to elucidate the aetiology behind the associations as well as clinical implications of the results.

2. Definition of Morphological Deviations of the Cervical Vertebral Column

The cervical vertebral column morphology of the upper five cervical vertebrae (C1–C5) on a lateral skull radiograph is divided into two main categories: "Fusion Anomalies" and "Posterior Arch Deficiency" according to Sandham, 1986 [43].

Fusion anomalies are fusion, block fusion, and occipitalization [43]. Fusion is defined as fusion of one unit with another at the articulation facets, neural arch, or transverse processes (Figure 1). Occipitalization is defined as assimilation, either partially or completely, of the atlas (C1) with the occipital bone (Figure 1). The definition of block fusion has been modified according to Sonnesen and Kjær [48] and defined as fusion of more than two units at the vertebral bodies, articulation facets, neural arch, or transverse processes.

Posterior arch deficiency consists of partial cleft and dehiscence according to Sandham, 1986 [43]. Partial cleft is defined as failure to fuse of the posterior part of the neural arch (Figure 1). Dehiscence is defined as failure to develop of part of a vertebral unit.

3. Association between Cervical Vertebral Column Morphology and Craniofacial Morphology

Sonnesen et al. have recently described morphological deviations of the cervical vertebral column in healthy subjects with neutral occlusion and normal craniofacial morphology [49, 50] and in patients with severe skeletal malocclusion traits such as skeletal deep bite, skeletal open bite, skeletal maxillary overjet, and skeletal mandibular overjet [48, 51–53]. It was found that morphological deviations of the cervical vertebral column such as fusion occurred significantly more often in patients with severe skeletal malocclusion traits when compared to controls. Fusion in the control groups occurred in 14–21 percent ($N = 3$–8), and fusions were always seen between the second and third cervical vertebrae [49, 50]. Fusion of the cervical vertebral column in the severe skeletal malocclusion groups occurred in 41–61 percent ($N = 17$–35). In the deep bite group, the open bite group, and in the horizontal maxillary overjet group, fusions were always seen between the second and third cervical vertebrae. The same pattern was seen in the control group [51–53]. The pattern of fusion in the mandibular overjet group differed from that of the control group as not only fusion occurred between the second and third cervical vertebrae but also block fusion between the second, third, and fourth cervical vertebrae [48]. In patients with condylar hypoplasia the pattern of fusion also differed as fusion between the third and fourth cervical vertebrae and occipitalization occurred [49]. These findings indicate an association between fusion of the cervical vertebral column and severe skeletal malocclusion.

A series of recent studies have focussed on the association between morphological deviations of the cervical vertebral

column and the craniofacial morphology in adult patients with severe skeletal malocclusion traits [48, 51–53]. These studies revealed that fusion of the cervical vertebral column had the closest association with craniofacial morphology. Significant associations between fusion and a large cranial base angle, between fusion and retrognathia of the jaws, and between fusion and inclination of the jaws were found in patients with severe skeletal malocclusions. The same pattern of craniofacial morphology was found in monozygotic twins when twins with fusion of the cervical vertebral column were compared with twins without fusion [50]. These findings indicate an association between fusion of the cervical vertebral column and the craniofacial morphology including the cranial base.

4. Association between Cervical Vertebral Column Morphology and Head Posture

An association between posture of the head and neck and the cervical vertebral column morphology has recently been demonstrated by Sonnesen et al. [49]. In individuals with neutral occlusion and normal craniofacial morphology, the cervical lordosis was significantly more curved and the inclination of the upper cervical column was more backwards in individuals with fusion than in individuals without fusion [49]. These findings indicate an association between fusion of the cervical column and posture of the neck.

5. Association between Cervical Vertebral Column Morphology and Sleep Apnoea

A study by Sonnesen et al. on cervical vertebral column morphology in patients with OSA [54] found a 46-percent ($N = 42$) prevalence of fusion anomalies in the cervical vertebral column. The deviations occurred significantly more often in patients with OSA and at a lower level in the cervical vertebral column compared to controls [54]. Fusion anomalies occurred as fusions either between the second and third vertebrae, between the third and fourth vertebrae, or between the fourth and fifth cervical vertebrae. Block fusions occurred as fusions either between the second, third, or fourth vertebrae, between the second, third, fourth, and fifth vertebrae, or between the third, fourth, and fifth vertebrae. Occipitalization occurred in combination with fusions, block fusions or as a single deviation [54].

The results of the studies on subjects with neutral occlusion and patients with severe skeletal malocclusions suggest that fusion of the cervical vertebral column is associated with occlusion, craniofacial morphology, and head posture. Furthermore, a different morphological pattern of the cervical vertebral column was found in patients with OSA.

6. Discussion

Associations between craniofacial morphology and head posture and between head posture and obstruction of the upper airways seen in patients with OSA have previously been demonstrated. Recent findings have established associations between craniofacial morphology including the cranial base and fusion of the cervical vertebral column, between head posture and fusion of the cervical vertebral column and between patients with OSA and fusion of the cervical vertebral column.

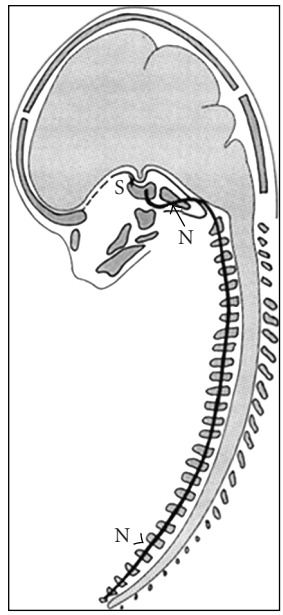


Figure 2: Illustration of the extension of the notochord (N). The black line indicates the caudocranial extension of the notochord through the vertebral bodies and the posterior part of the cranial base.

An explanation for the association between fusion of the cervical column and a large cranial base angle could be found in the early embryogenesis. The notochord develops in the human germ disc and determines the development of the cervical vertebrae, especially the vertebral bodies, and also the basilar part of the occipital bone in the cranial base [55–59] (Figure 2). The para-axial mesoderm forming the vertebral arches and remaining parts of the occipital bone are also formed from notochordal inductions. Therefore, a deviation in the development of the notochord may influence the surrounding bone tissue in the vertebral column as well as in the posterior part of the cranial base. It can be observed on postnatal profile radiographs that the bone tissue formed around the notochord is the vertebral bodies and the basilar part of the occipital bone. The shared origin of the vertebral column and the posterior part of the cranial base supports the new hypothesis that associations between the cervical vertebral column and the cranial base exist [60, 61].

The association between fusion of the cervical column and the craniofacial morphology could also be explained by the early embryogenesis. It is known that the neural crest cells migrate to the craniofacial area before the notochord is surrounded by bone tissue and disappears [55, 57–59, 61,

62]. The jaws, including the condylar cartilage, develop from ectomesenchymal tissue derived by the neural crest. In the first branchial arch the neural crest cells migrate from the neural crest towards the mandible, followed by the cells to the maxilla and lastly by the cells to the nasofrontal region [57]. Therefore, it is understandable that a deviation in the amount or timing of migrating maxillary and mandibular cells may influence the craniofacial development [53]. The precise signalling from the notochord to the neural crest followed by bilateral cell migration to the craniofacial area is still unknown. Signalling during early embryogenesis between the notochord, para-axial mesoderm, the neural tube, and the neural crest may explain the association between the cervical vertebral column, cranial base, and craniofacial development [61].

The study on patients with obstructive sleep apnoea found that the prevalence of fusion anomalies of the cervical vertebral column occurred significantly more often in patients with OSA and at a lower level in the cervical vertebral column compared to controls [54]. These deviations in prevalence and pattern of the cervical vertebral column may prove a factor in the pathogenetic background of sleep apnoea and thereby contribute to the diagnosis and treatment of patients with OSA [54].

7. Conclusions

Recent findings have demonstrated associations between craniofacial morphology including the cranial base and fusion of the cervical vertebral column, between head posture and fusion of the cervical vertebral column and between patients with OSA and fusion of the cervical vertebral column. Accordingly, the results of these studies suggest that fusion of the cervical vertebral column is associated with the development and function of the craniofacial morphology. The morphological pattern of the upper cervical vertebrae is expected to be of importance for diagnostics and the elucidation of aetiology and thereby for the optimal treatment of patients with severe skeletal malocclusions and patients with OSA.

These associations between the cervical vertebral column, the cranial base, and the craniofacial morphology suggest a new hypothesis: signalling during early embryogenesis between the notochord, para-axial mesoderm, the neural tube, and the neural crest explains these associations between the cervical vertebral column, the cranial base, and the craniofacial skeleton.

It is suggested that dentists look at the cervical vertebral column area and register any deviations in the cervical vertebral column morphology and head posture. These registrations may prove useful when considering diagnosis and evaluating aetiology, especially in patients with severe skeletal malocclusions and OSA.

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Review Article

The Prevalence of Concha Bullosa and Nasal Septal Deviation and Their Relationship to Maxillary Sinusitis by Volumetric Tomography

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The objective of this study was to determine the prevalence of concha bullosa and nasal septal deviation and their potential relationships to maxillary sinusitis. 883 CT scans taken at Creighton University School of Dentistry from 2005 to 2008 were retrospectively reviewed for the presence of concha bullosa, nasal septal deviation, and maxillary sinusitis. 67.5% of patients exhibited pneumatization of at least one concha, 19.4% of patients had a deviated septum, and 50.0% had mucosal thickening consistent with maxillary sinusitis. 49.3% of patients who had concha bullosa also had evidence of maxillary sinusitis. Only 19.5% of patients with concha bullosa also had nasal septal deviation, whereas 19.7% of patients with sinusitis also presented with nasal septal deviation. Although concha bullosa is a common occurrence in the nasal cavity, there did not appear to be a statistically significant relationship between the presence of concha bullosa or nasal septal deviation and maxillary sinusitis.

1. Introduction

With the recent widespread introduction of cone beam computed tomography (CBCT), dentists and otolaryngologists are better able to identify anatomical abnormalities and pathological states within the structures of the nasal cavity and the surrounding paranasal sinuses. Previously used radiographic techniques were frequently less effective at identifying irregularities in the sinuses [1]. Mucosal inflammation can be easily identified in computed tomography (CT) scans, arguably making this radiographic modality the standard for accurately evaluating the nasal cavity and paranasal sinuses [1].

On each side of the nasal cavity, there exists a superior, middle, and inferior concha. It is widely believed that osteomeatal obstructions may impede ventilation and mucociliary clearance from the sinuses, predisposing affected patients to sinus disease [1]. Less is understood about the role of a deviated septum or pneumatization of the conchae as potential contributors to the development of sinusitis [2]. While some studies suggest that deviations of the nasal septum or the presence of concha bullosa may interfere with proper airflow, potentially predisposing to sinus disease, other studies have produced contradictory findings [1, 3, 4]. The purpose of this study was to determine the prevalence of concha bullosa and nasal septal deviation and to examine their possible relationship to maxillary sinus disease.

2. Materials and Methods

A retrospective study was conducted of 883 CBCT scans taken between September 2005 and June 2008 at Creighton University School of Dentistry (Omaha, NE). This study was exempt from review by the Institutional Review Board. All scans were taken using an iCAT CBCT scanner (Imaging Sciences International) at a 0.3 mm voxel size. Scans were reconstructed using Osirix software and evaluated in the axial, sagittal, and coronal planes. Two trained investigators, well versed on the anatomy of the region, independently reviewed

Table 1: Age distribution of the male and female population.

Age range (years)	Gender	
	Male	Female
1–10	9	12
11–20	49	46
21–30	83	75
31–40	40	34
41–50	41	86
51–60	70	107
61–70	55	77
71–80	22	36
81–90	11	13
91–100	0	1
Mean	42.8	46.7
Standard Deviation	20.2	19.7

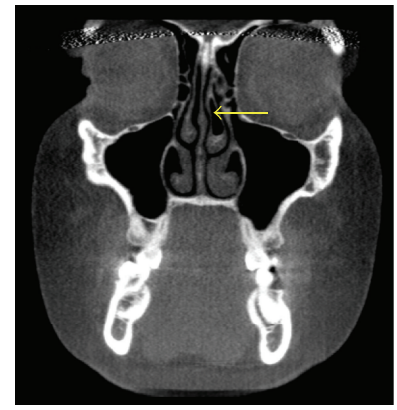

Figure 1: Coronal CT scan demonstrating the presence of left middle concha bullosa (arrow). No septal deviation or sinusitis is present. Note the size difference in the middle conchae, with the left middle concha larger than the right middle concha.

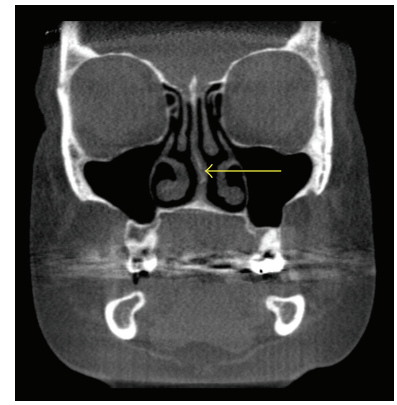

Figure 2: Coronal CT scan demonstrating left nasal septal deviation (arrow). No concha bullosa or sinusitis is evident.

the scans. Any contradictory findings were reviewed by an anatomist. The gender and age of the patient were the only patient-specific variables included in this study.

Scans were reviewed for any nasal cavity and/or paranasal anatomical abnormalities, with specific evaluation on the presence of concha bullosa, deviated septa, and sinusitis of the maxillary sinuses. Concha bullosa was defined as the presence of pneumatization of any size within in the superior, middle, or inferior conchae. Septal deviation was defined as a deviation of greater than 4 mm from the midline. The presence of any radiographic mucosal thickening above the bony floor of the maxillary antrum was defined as abnormal [1, 4]. Data was analyzed with a Chi-square test using the SAS 9.1 program.

3. Results

Table 1 summarizes the age and gender distribution of the patient population examined. The mean age of the patients was 44.2 years of age, with a range of 4 to 99 years. Of the 883 scans evaluated, 43.6% were from male patients and 56.3% were female patients.

67.5% of the patient scans reviewed had evidence of pneumatization of the concha. From the 883 scans, 12.3% were located in one of the right conchae, 13.0% involving the left conchae, and 43.2% bilaterally distributed. The majority of concha bullosa were located in the middle concha; 7.8% on the right side, 8.3% left (Figure 1), and 20.8% bilateral. In the concha bullosa group, 56.3% were female and 43.7% were males ($P = .856$). The mean age of patients with concha bullosa (45.6 years of age) was similar to the overall study population (Table 2).

19.4% of patients had deviated septa (Figure 2). There was no statistical difference between gender and the presence of nasal septal deviation (19.9% female; 18.9% were male; $P = .703$, Table 2).

A total of 50.0% of patients had evidence of maxillary sinusitis. There was a statistically significant higher prevalence of maxillary sinusitis in males (61.8%) compared to females (41.8%; $P < .0001$). 12.1% had right maxillary sinusitis, 15.6% had left-sided involvement, and 21.0% had bilateral sinus disease (Figure 3). The mean age of patients with sinusitis was 44.3 (Table 2).

There was no statistical significance when comparing the relationship of patients with concha bullosa (67.6%) and those with sinusitis (41.8%). 49.3% of patients had a combination of both (Figures 4, 5, and 6), 50.7% had concha bullosa without evidence of sinusitis, and 33.5% had sinusitis in the absence of concha bullosa ($P = .533$, Table 3).

The relationship between unilateral or bilateral concha bullosa and ipsilateral sinusitis was not statistically significant. Of the 109 patients with right concha bullosa, only 12.8% also had right maxillary sinusitis ($P = .804$). Of the 115 patients with left concha bullosa, only 18.3% of patients also demonstrated left maxillary sinusitis ($P = .426$). Of the 381 patients with bilateral concha bullosa, only 21.3% of patients had maxillary sinusitis ($P = .559$, Table 4).

The relationship between the presence of concha bullosa and nasal septal deviation was not statistically significant. Of the 596 patients with concha bullosa, 19.5% also had

Table 2: Prevalence and gender distribution of concha bullosa, nasal septal deviation, and sinusitis.

	Concha Bullosa		Nasal Septal Deviation		Sinusitis	
	Present	Absent	Present	Absent	Present	Absent
Total	596 (67.5%)	278 (31.4)	171 (19.4%)	712 (88.6%)	442 (50.0%)	441 (50.0%)
Gender						
Male	261 (68.3%)	121 (31.7%)	73 (18.9%)	310 (81.2%)	236 (61.8%)	146 (38.2%)
Female	334 (67.8%)	159 (32.3%)	98 (19.9%)	395 (80.1%)	206 (41.8%)	287 (58.2%)

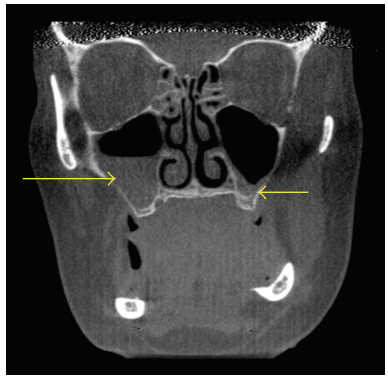

Figure 3: Coronal CT scan demonstrating bilateral maxillary sinusitis (arrows). The degree of sinus inflammation is more prominent in the right sinus. Concha bullosa or nasal septal deviation are not noted.

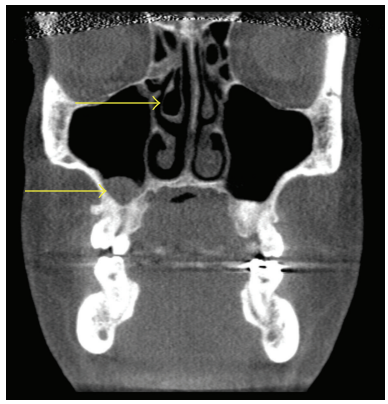

Figure 4: Coronal CT scan demonstrating right middle concha bullosa (superior arrow) and right maxillary sinusitis (inferior arrow). No nasal septal deviation is present. Note the difference in size of the right middle concha compared to the left middle concha.

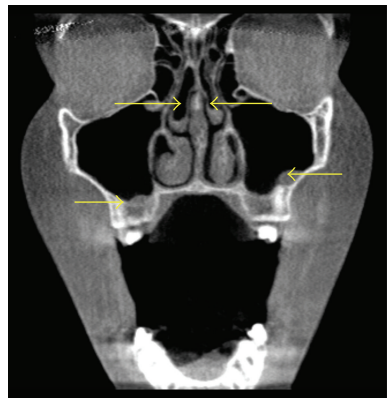

Figure 5: Coronal CT scans demonstrating bilateral middle concha bullosa (superior arrows) with bilateral maxillary sinusitis (inferior arrows). Note that there is more mucosal thickening on the left floor of the maxillary sinus than the right sinus floor, whereas the right concha bullosa demonstrates a greater degree of pneumatization compared to the left concha bullosa.

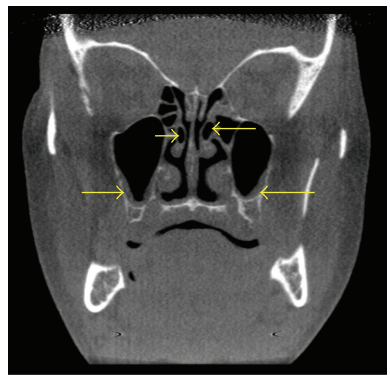

Figure 6: Coronal CT scan demonstrating bilateral middle concha bullosa (superior arrows) in combination with bilateral maxillary sinusitis (inferior arrows). Note the left concha bullosa (right superior arrow) is located slightly superior to the left concha. There is similar degree of sinus inflammation in both maxillary sinuses.

deviation of the nasal septum (Figure 7). 80.5% of patients had concha bullosa without a deviated septum. 32.2% of the 171 patients with a deviated septum had no evidence of concha bullosa ($P = .916$; Table 5).

Examining the potential relationship between sinusitis and nasal septal deviation, there was no statistical significance. 87 (19.7%) of the 442 patients with maxillary sinusitis also had nasal septal deviation (Figure 8). 355 (80.3%) of the patients with maxillary had no deviated septum. 84 (49.1%) of 171 patients with deviated septum had no evidence of maxillary sinus disease ($P = .811$; Table 6).

4. Discussion

In our study, 67.5% of patients had concha bullosa, which is somewhat higher than other studies, in which the prevalence of concha bullosa varied from 35% to 53% [1–4]. This

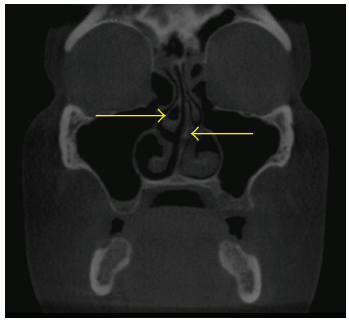

Figure 7: Coronal CT scan demonstrating right middle concha bullosa (left arrow) and left nasal septal deviation (right arrow). No sinus inflammation is present. Also note the differences in shape of the concha: the right middle concha is larger than the left middle; the left inferior concha is larger than the right inferior concha.

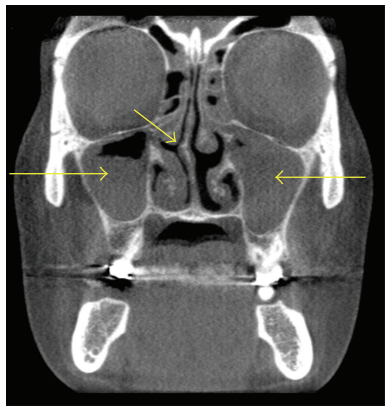

Figure 8: Coronal CT scan demonstrating right nasal septal deviation and severe bilateral maxillary sinusitis. No concha bullosa is present. The left maxillary sinus has a greater degree of inflammatory involvement than the right sinus.

Table 3: Relationship of concha bullosa and sinusitis.

		Concha Bullosa	
		Present	Absent
Sinusitis	Present	294 (49.3%)	148 (16.7%)
	Absent	302 (50.7%)	139 (15.7%)

Table 4: Relationship of right, left, or bilateral concha bullosa, compared to the presence of ipsilateral sinusitis.

Concha Bullosa	Ipsilateral Sinusitis present
Right	14/109 (12.8%)
Left	21/115 (18.3%)
Bilateral	81/381 (21.3%)

variation may be due to differing criteria used to define concha bullosa. In our study, we defined any degree of pneumatization, regardless of size or location, as consistent with concha bullosa. Other studies restricted concha bullosa to specific locations on the turbinates and/or to a minimum size of pneumatization [1, 3, 4]. In Subramanian's study [4], there was a higher incidence of concha bullosa in females (58.9%) compared to males.

Table 5: Relationship of concha bullosa and nasal septal deviation.

		Concha Bullosa	
		Present	Absent
Septal Deviation	Present	116 (19.5%)	55 (19.2%)
	Absent	480 (80.5%)	116 (19.5%)

Table 6: Relationship of concha bullosa and sinusitis.

		Concha Bullosa	
		Present	Absent
Sinusitis	Present	87 (19.7%)	355 (80.3%)
	Absent	84 (19.1%)	357 (80.95%)

19.4% of patients in our study had nasal septal deviation, which is significantly lower than Stallman's 65% [3] and Sazgar's [2] 62.9% prevalences. The reason for this difference is most likely due to our stricter criteria for classification as deviated septum, which we defined as a deviation of greater than four millimeters from the midline. Stallman et al. [3] subjectively categorized deviations as mild, moderate, or severe, and Sazgar et al. [2] defined septal deviation as any asymmetric curvature of the septum.

Sinusitis, which was defined in our study as any evident thickening of the mucosa in the maxillary sinus, occurred in 50.0% of our patient population. Bolger's study [1] noted mucosal thickening of the sinus floor in 83.2% of patients. While the difference may be the result of referral bias (our patients were primarily referred for radiographic assessment prior to dental implant placement and not evaluation of suspected sinus disease), other potential variations such as seasonal bias, in which a small consecutive patient sample is chosen during a season that may predispose patients to higher incidence of allergies, may have contributed to this discrepancy. Our study was conducted over 2.5 years, spanning all seasons. One significant finding in our study was the relationship between sinusitis and gender, with males having a 20.0% higher incidence of sinusitis. Such a difference may be due to anatomical variations or mucosal secretion differences between the sexes.

While it has been suggested that abnormalities of the concha can predispose patients to obstruction of the sinuses, leading to chronic sinusitis [4–6], other studies with findings similar to those in the current study concluded that there was no correlation between the presence of concha bullosa and sinusitis [3, 5, 7]. Previous studies that supported the validity of a relationship have typically included a majority of patients with pre-existing chronic sinusitis [4].

While studies have suggested an association between septal deviation and the presence of concha bullosa [2, 3], the presence of septal deviations was usually associated with the presence of dominant or large concha bullosa [2, 3]. However, in our study, only 19.5% of patients with septal deviation had concha bullosa, suggesting that in many cases there is no relationship.

Regarding any potential relationship between nasal septal deviation and sinusitis, Hatipoglu et al. [8] found that there was an association between the degree of deviation and the presence of sinusitis. However, a meta-analysis conducted by Collet et al. [9] failed to confirm a definite relationship between these 2 factors, which is in agreement with the current study.

5. Conclusion

We found no definitive relationship between the presence of concha bullosa or nasal septal deviation and the development of maxillary sinusitis.

Acknowledgment

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Case Report

Ameloblastic Fibro-Odontoma: A Diagnostic Challenge

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An 11-year-old girl presented to our department to have a second opinion regarding a lesion involving her left mandible. She had previously undergone several radiographic exams including panoramic, helical, and cone-beam computed tomography. Radiographic examinations revealed a well-defined radiolucent region, which contained an irregular radiopaque mass of 3 cm in diameter, localized to the left angle of the mandible. Our presumptive diagnosis was complex odontoma. Excisional biopsy was performed, and microscopic features showed strands and islands of odontogenic epithelium showing peripheral palisading and loosely arranged central cells, identical to stellate reticulum, embedded in a myxoid cell-rich stroma resembling the dental papilla. Dentin and enamel were also presented. The diagnosis was ameloblastic fibro-odontoma, which is a rare mixed odontogenic tumor, derived from epithelial and ectomesenchymal elements that form the dental tissues.

1. Introduction

Ameloblastic fibro-odontoma (AFO) is a benign, slow growing, expansile epithelial odontogenic tumor with odontogenic mesenchyme. It may inhibit tooth eruption or displace involved teeth although teeth in the affected area are vital [1–3]. Radiography shows a well-defined, radiolucent area containing various amounts of radiopaque material of irregular size and form [4, 5]. The lesions are usually diagnosed during the first and second decades of life [4–6]. It occurs with equal frequency in the maxilla and the mandible and with equal frequency in males and females [6].

Microscopically, the lesion is composed of strands, cords, and islands of odontogenic epithelium embedded in a cell-rich primitive ectomesenchyme, resembling the dental papilla. Many authors reported that AFO is not aggressive and can be treated adequately through a surgical curettage to the lesion without removal of the adjacent teeth [1, 4, 5, 7, 8]. This paper describes an extensive AFO in an 11-year-old girl.

2. Case Description

An 11-year-old girl presented to our department on referral from another dentist to have a second opinion about a lesion involving the left mandible. She had radiographic examinations, including panoramic, helical, and cone-beam computed tomography. These examinations were accompanied by a presumptive radiographic differential diagnosis of "odontoameloblastoma": complex odontoma and AFO.

The medical, social and family histories were unremarkable, as were the results of a review of systems and a physical examination. The clinical examination did not display any sign of pain or swelling in the left mandible. There was no history of local trauma or infection. Oral inspection revealed good oral hygiene.

The initial panoramic radiography revealed a well-defined radiolucent region, which contained an irregular radiopaque mass 3 cm in diameter. This lesion occupied a zone from the lower left second molar area to the left ramus. The mandibular left second molar was not present (Figure 1).

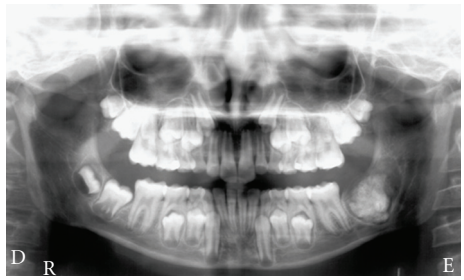
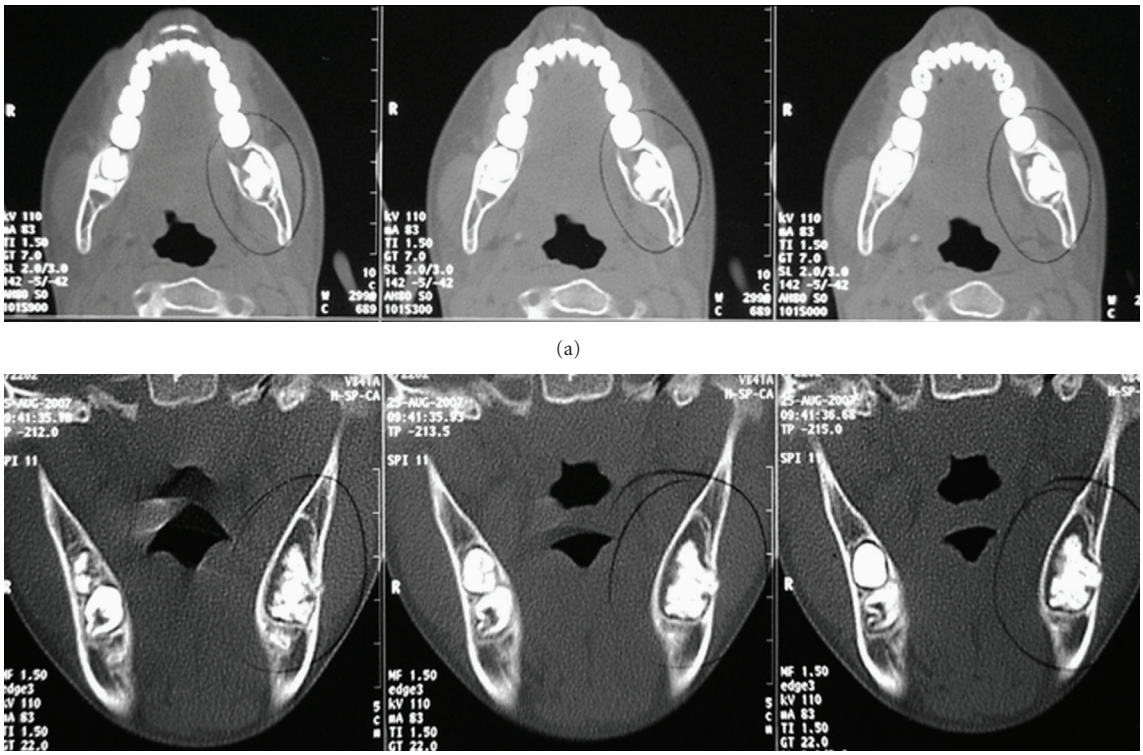


Figure 1: Initial panoramic radiography showing well-defined radiolucent region, which contained an irregular radiopaque mass measuring 3 cm in diameter. This lesion occupied a zone from the lower left second molar area to the left ramus.



(a)

(b)

Figure 2: Helical computed tomography images showing an expansile, well-circumscribed lesion containing a calcified mass compatible with odontogenic tissue ((a) axial cuts; (b) coronal cuts).

Helical and cone-beam computed tomography showed an expansile well-circumscribed lesion containing at the interior a calcified mass compatible with odontogenic tissue (Figures 2 and 3).

Considering the clinical and radiographic examinations, our presumptive diagnosis was complex odontoma.

The patient underwent enucleation of the lesion and careful curettage of the surgical cavity under general anesthesia. The surgical specimen was fixed in neutral buffered 10% formalin and subjected to pathological analysis. Light microscopic examination of sections stained with hematoxylin and eosin revealed strands and islands of odontogenic epithelium showing peripheral palisading and loosely arranged central cells, identical to stellate reticulum, embedded in a myxoid cell-rich stroma resembling the dental papilla (Figure 4). Dentin and enamel were also present (Figure 5). The final diagnosis was AFO. The patient is being followed up postoperatively and there is no sign of recurrence.

3. Discussion

In the present case, the patient presented to our department with previous examinations, including panoramic, helical and cone-beam computed tomography. While these radiographic examintions were given a presumptive diagnosis of odontoameloblastoma by the examinaing radiologists, we believed that the findings were more common in this region. Odontoameloblastoma, also known as ameloblastic

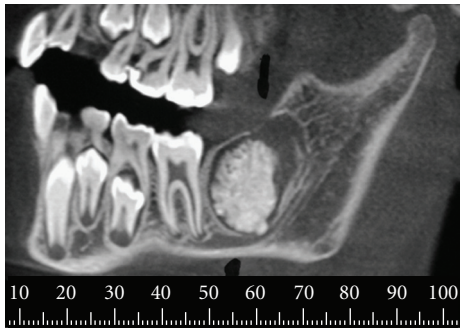


Figure 3: Cone-beam tomography (panoramic reconstruction) showing a well-circumscribed calcified mass in intimate contact with the alveolar inferior nerve.

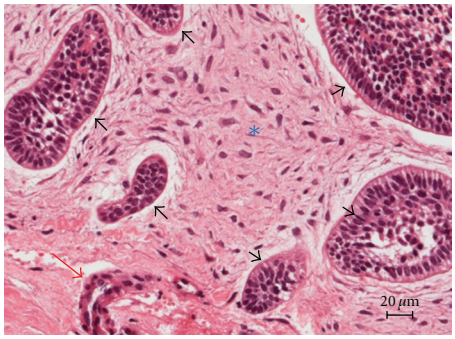


Figure 4: (H.E.) Strands (red arrow) and islands (black arrows) of odontogenic epithelium showing peripheral palisading and loosely arranged central cells, identical to stellate reticulum embedded in myxoid cell-rich stroma resembling the dental papilla (*).

odontoma, has a more aggressive behavior, similar to an ameloblastoma rather than an odontoma [9].

The histogenesis of this lesion is controversial. AFO is a benign tumor that exhibits the same benign biologic behavior as that of ameloblastic fibroma, showing inductive changes that lead to the formation of both dentin and enamel [1]. This is in contrast to the ameloblastoma. Conversely, the term "odontoameloblastoma" (or "ameloblastic odontoma") refers to tumors representing a histological combination of ameloblastoma and complex odontoma, which behave in the invasive manner of classic ameloblastoma [6].

According to the revised World Health Organization (WHO) classification [10], ameloblastic fibroma and AFO are believed to be stages of complex odontoma formation [1]. This means that the aforementioned lesions should not be considered as distinct entities [11]. Cahn and Blum [13] postulated that ameloblastic fibroma (the histologically least differentiated tumor) develops first into a moderately differentiated form, following AFO and eventually into a complex odontoma. However, the concept that these lesions represent a continuum of differentiation is not widely accepted, with other researchers suggesting that they are separate pathologic entities [12–15]. In some studies, the term AFO represents a histological combination of ameloblastic fibroma and complex odontoma [12, 16]. The majority now agrees that

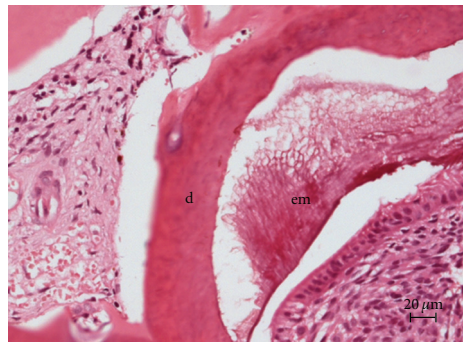


Figure 5: (H.E.): Dentin (d) and enamel matrix (em).

AFO exists as a distinct entity, but it can be histologically indistinguishable from immature complex odontoma. The arrangement of the soft tissues and the development stage of the involved tooth are useful criteria for diagnosis [3]. Despite numerous efforts, however, there is still considerable confusion concerning the nature of these lesions [17].

AFO is relatively rare, with the prevalence among oral biopsies being about 1% [4] and its frequency among odontogenic tumors being reported at 1% to 3% [3, 18]. This lesion usually occurs in people less than 20 years old, and age is thus an important characteristic in the differential diagnosis. This lesion is usually found in the molar area [6, 12], and the distribution is roughly equal between the maxilla and mandible [6, 12].

Many authors reported that AFO can be treated adequately through a surgical curettage without removal of the adjacent teeth [1, 4, 5, 7, 8]. As noted in the literature, not all lesions previously classified as AFO are, in fact, aggressive lesions. If there is a recurrence accompanied by a change of the histological pattern toward a more unorganized fibrous stroma with displacement of the epithelial component, then more extensive treatment procedures appear to be indicated [19]. Determination of a case-dependent treatment plan may provide an optimum outcome. Long-term follow up with short intervals should be maintained in the management of AFO.

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