UNIVERSIDADE ESTADUAL DE CAMPINAS
FACULDADE DE ODONTOLOGIA DE PIRACICABA

EDUARDO RODRIGUES FREGNANI
Cirurgião-Dentista

Avaliação epidemiológica de 8.875 diagnósticos histopatológicos orais realizados pelo Serviço de Diagnóstico Oral da Disciplina de Patologia Bucal da FOP/UNICAMP em um período de 32 anos.

Dissertação apresentada à Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas, para obtenção do Título de Mestre Estomatopatologia, Área de Patologia.

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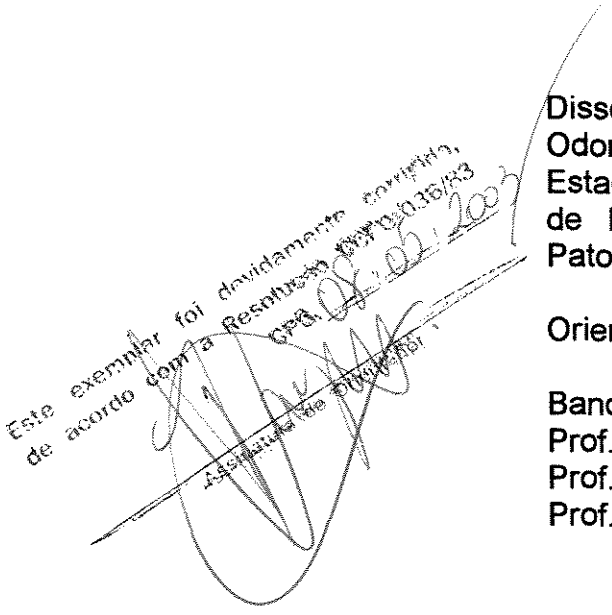

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Orientador : Prof. Dr. Pablo Agustin Vargas

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Prof. Dr. Pablo Agustin Vargas
Prof. Dr. Halbert Villalba
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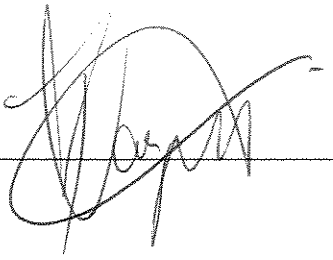
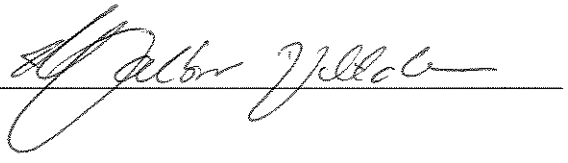
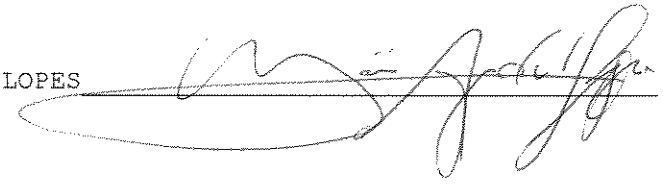
A Comissão Julgadora dos trabalhos de Defesa de Tese de MESTRADO, em sessão pública realizada em 27 de Fevereiro de 2003, considerou o candidato EDUARDO RODRIGUES FREGNANI aprovado.

1. Prof. Dr. PABLO AGUSTIN VARGAS 

2. Prof. Dr. HALBERT VILLALBA 

3. Prof. Dr. MARCIO AJUDARTE LOPES 

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Epígrafe

"Transportai um punhado de terra todos os dias

e fareis uma montanha".

Confúcio

Sumário

Resumo

Estudos epidemiológicos de doenças orais são importantes para verificar a prevalência relativa de lesões reativas, infecciosas, císticas e neoplásicas e, para determinar estratégias de prevenção e tratamento. A freqüência de lesões orais possui diferenças geográficas, sendo importante obter informações não somente dos países, mas também de suas sub-regiões. Por exemplo, o Brasil possui enormes diferenças econômicas, culturais e demográficas entre suas regiões o que pode refletir em diferentes prevalências de lesões orais. Assim, este trabalho, composto por dois artigos, teve como objetivos: 1- analisar a freqüência dos 8.875 casos de doenças bucais encaminhados ao Serviço de Diagnóstico Oral da FOP/UNICAMP num período de 32 anos; 2- verificar especificamente a freqüência dos Tumores Odontogênicos (TO) no mesmo período. 3- Desenvolver um banco de dados informatizado com a finalidade de agrupar os dados e facilitar a análise da casuística. A metodologia utilizada em comum para os dois artigos consistiu na revisão histológica e revisão dos dados clínicos disponíveis por dois examinadores, lançamentos dos dados no *software* desenvolvido e posterior estudo epidemiológico. Como resultados do primeiro trabalho, verificou-se que a maioria dos casos foram lesões reativas ou infecciosas tais como hiperplasias fibrosas (26%), lesões periapicais (11%) e periodontites (10%). O carcinoma espinocelular foi responsável por 5% dentre todos os casos e 86% de todas as neoplasias malignas. Paracoccidioidomicose mostrou um grande número de

casos (150) e os TO representaram 1,26% do total. Como resultados do segundo trabalho, diagnosticamos 113 casos de TO, sendo 39,4% odontomas, 22,1% ameloblastomas e apenas um caso maligno (Ameloblastoma maligno). Além disso, os TO ocorreram predominantemente entre a 2ª e 3ª décadas de vida e a região posterior da mandíbula foi o local anatômico mais acometido para os ameloblastomas e região anterior de maxila para os odontomas.

Abstract

Epidemiological studies of oral diseases are important to verify the relative prevalence of reactive, infectious, cystic and neoplastic lesions, and to determine strategies of prevention and treatment. Moreover, geographical differences may lead to clues regarding the causes of these lesions. Frequency of oral diseases varies throughout the world, and it is important to have information not only of countries, but also of each specific region. For example, Brazil has enormous differences among its regions relating to economical, cultural and demographic aspects that may reflect different prevalence of oral lesions. So, the purpose of this study, presented as two distinct publications, is to: 1. - show the frequency of 8,875 oral and perioral lesions submitted to the Oral Diagnostic Service of the Oral Pathology Department at the School of Dentistry of Piracicaba – UNICAMP, Brazil during a 32-year period; 2 – to verify particularly the Odontogenic Tumors frequency at the same period of time; 3- a computer database software was developed to collect and store the data. The assessment method consisted of reviewing all microscopic slides and available clinical data by two examiners; data storage on the developed software and finally, the epidemiological analysis. As a result of the first work, it could be seen that the majority of the oral biopsies were taken from either infectious or reactive lesions as fibrous hyperplasias (26%), periapical lesions (11%) and periodontitis (10%). Squamous cell carcinoma was responsible for 5% of the total cases and corresponded to 86% of all malignant neoplasms. It is interesting to notice the

occurrence of 150 cases of paracoccidioidomycosis. Odontogenic tumours corresponded to 1.26% of the total. As for the results of the second article, it is noticed that among the 113 Odontogenic Tumors cases, 39.4% were odontomas, 22.1% ameloblastomas and only one malignant case, diagnosed as malignant Ameloblastoma. In addition, the cases occurred predominantly in the second and third decades of life, and the posterior region of the mandible was the most affected site to ameloblastomas whereas anterior maxilla was to odontomas.

1. Introdução

Epidemiologia é a ciência que estuda o processo saúde-doença na sociedade, analisando a distribuição populacional e os fatores determinantes das enfermidades, danos à saúde e eventos associados à saúde coletiva, propondo medidas específicas de prevenção, controle ou erradicação de doenças e fornecendo indicadores que sirvam de suporte ao planejamento, administração e avaliação das ações de saúde. (ALMEIDA FILHO. & ROUQUAYROL,1990)

Iniciou-se a partir dos estudos de grandes epidemias como a peste bubônica, cólera e varicela, que ocorreram em ondas caracterizadas por altas taxas de mortalidade.

Os estudos epidemiológicos apresentam variações na prevalência de doenças em diferentes partes do mundo devido a fatores sociais, econômicos, culturais e ambientais. A obtenção de dados estatísticos referentes a diversas enfermidades nos permite ter, atualmente, índices epidemiológicos do câncer, das cardiopatias, das doenças infecciosas e inúmeras outras doenças. Da mesma forma, o conhecimento da prevalência de doenças e alterações bucais tem importância para epidemiologistas, para a saúde pública e para os profissionais da área de saúde, permitindo o planejamento da abordagem terapêutica adequada para cada doença.

Estima-se que em um serviço de Histopatologia Geral menos de 5% do total de biópsias são provenientes de Patologia Oral (BARRET & SPEIGHT, 1996). Estes autores também verificaram que a maioria dos patologistas

considera útil a especialidade de patologia oral, visto que geralmente consultam um especialista nos diagnósticos de doenças de mucosa bucal, tumores odontogênicos e de glândulas salivares.

Além disso, nas últimas décadas triplicou o número de biópsias realizadas pelos Cirurgiões-Dentistas, aumentando a tendência de dentistas enviarem para exame histopatológico as lesões com suspeitas de malignidade ou que clinicamente ofereçam maiores dificuldades de diagnóstico.

As Faculdades de Odontologia são, naturalmente, os centros onde os Serviços de Patologia Bucal estão organizados e especializados, e para onde a maioria dos casos são encaminhados.

Assim, pareceu-nos oportuno avaliar e revisar os diagnósticos histopatológicos orais enviados ao Serviço de Diagnóstico Oral da FOP/UNICAMP em um período de 32 anos e, então, obter os índices epidemiológicos das doenças bucais em nossa região.

2. Revisão de Literatura

A revisão de literatura foi dividida em duas partes. Primeiramente, foram relatados os trabalhos que analisaram grande número de biópsias de região orofacial, representando estudos epidemiológicos similares aos propostos no presente estudo. A segunda parte, complementar, mostra alguns estudos que tiveram como objetivo determinar a freqüência e distribuição de determinados grupos de doenças ou em determinadas populações, como por exemplo, tumores odontogênicos e pacientes pediátricos, respectivamente.

2.1 PARTE I

Estudos epidemiológicos de biópsias da região orofacial

Em 1968, BHASKAR relatou 288 tipos de lesões da cavidade bucal em 20.575 biópsias de boca. As lesões periapicais, como granulomas e cistos foram as mais freqüentes correspondendo a 24% dos casos. Foram descritos 187 casos de leucoplasias e 41 de eritroplasias, correspondendo a 1,25% de todas as biópsias. Cisto dentígero e tumores odontogênicos corresponderam a 6,56% e 2,37%, respectivamente. O autor também salientou a importância do diagnóstico bucal inicial de doenças como pênfigo, leucemia, líquen plano e doença de Paget.

HAPPONEN *et al.* (1982) analisaram 15.758 biópsias realizadas por dentistas na Finlândia durante o período de 1974 a 1981. Os dez diagnósticos mais comuns somaram 82,5% de todo o material, destacando-se cisto radicular (33,8 %), granulomas e abscessos periapicais (24,5%). Apenas 71 casos de lesões pré-malignas e malignas foram obtidos, sendo que o carcinoma espinocelular correspondeu por 50,7% das lesões malignas. Essa baixa porcentagem de casos de carcinoma espinocelular pode ser explicada pelo fato de o estudo ter sido realizado na Finlândia, um país desenvolvido, no qual, programas preventivos podem ser realizados quando se sabem seus agentes etiológicos.

Em 1983, ZANCANARO & LORANDI avaliaram os tipos de lesões mais comumente enviadas a exame histopatológico do serviço de Estomatologia da Pontifícia Universidade Católica do Rio Grande do Sul - PUC/RS. O trabalho considerou os diagnósticos histopatológicos do período de 1977 a 1982 totalizando 4.914 casos. As inflamações crônicas compreenderam 47,86% dos casos, lesões císticas equivaleram a 10,6%, neoplasias benignas por 6,91% e as malignas a 2,4% dos casos.

ALMEIDA *et al.* (1987) realizou o levantamento de lesões bucais examinadas no Serviço Médico de Anatomia Patológica da cidade de Piracicaba. Os casos de boca e região peribucal corresponderam a 1.211 casos (2,2%) do total (54.845 casos). 56% das alterações não eram neoplásicas, 14,6% eram neoplasias benignas e 29,4% neoplasias malignas. O fato do estudo ter sido realizado em um serviço médico onde a maior parte do material

é proveniente de hospitais, pode ser o fator dessa maior prevalência de neoplasias malignas quando comparada aos demais estudos. O carcinoma espinocelular correspondeu a 293 casos, sendo mais comum no lábio inferior, no sexo masculino e em pacientes entre 50-60 anos de idade.

SKINNER *et al.* (1987) publicaram trabalho determinando parâmetros epidemiológicos de lesões orais entre pacientes idosos. Por um período de 16 anos, 13.378 biópsias foram analisadas pelo serviço de anatomia patológica da Universidade da Louisiana, EUA. Entre essas biópsias, 3354 (25%) eram de pacientes com idade superior a 55 anos de idade. Foram feitos 157 diagnósticos diferentes. As lesões mais comumente vistas neste grupo foram hiperplasias fibrosas (17,5%), hiperqueratoses (8,9%), doenças periodontais (8,7%) e inflamações periapicais (7,8%). Significantemente, 11% das biópsias deste segmento da população eram malignas (6,6%) ou pré-malignas (4,4%). Vale destacar que um número maior de biópsias foi realizada em mulheres (61%) do que em homens (39%).

Em 1987, WEIR *et al.* estudaram 15.783 lesões orais coletadas em seu serviço. Os diagnósticos mais comuns foram fibroma (13,2%), granuloma periapical (8,0%), mucocele (6,0%), periodontite (6,0%), cisto radicular (5,8%) e cisto dentígero (4,2%).

Vale destacar o trabalho de LAYFIELD *et al.* (1995) que através de microcomputadores determinaram parâmetros epidemiológicos e a incidência das 30.056 biópsias encaminhadas ao serviço de Diagnóstico da Universidade Estadual da Lousiana. Os resultados mostraram que 12,8% das biópsias orais

eram de gengiva e que suas lesões mais freqüentes foram doença periodontal, hiperplasia fibrosa, granuloma piogênico e fibroma ossificante periférico. Neoplasias benignas e malignas perfizeram 15,5% do total.

O trabalho de CHIDZONGA *et al.* (1996) realizado na população de Zimbabwe descreveu 1.723 biópsias orofaciais coletadas durante um período de 10 anos. 55,9% dos casos da revisão eram de origem não odontogênica, sendo 39,3% carcinoma espinocelular, enquanto que 79,1% das lesões odontogênicas eram ameloblastomas. Ao contrário do estudo de HAPPONEN *et al.* (1982) na Finlândia, que mostrava poucos casos de carcinoma espinocelular, este estudo realizado na África mostra que políticas preventivas ao carcinoma espinocelular não são realizadas.

TAY (1999) realizou levantamento das biópsias orais realizadas em um centro de cirurgia oral em Cingapura. Foram revisados 2.057 casos, concluindo que hiperplasia fibrosa (10,3%), granuloma periapical (8,8%) e mucocele (8,6%) foram os diagnósticos mais comuns. 3,5% correspondiam a carcinoma espinocelular, 2,4% a queratocistos e 1,8% a ameloblastomas.

A seguir, a tabela I mostra, cronologicamente, estudos epidemiológicos de doenças bucais a partir da avaliação histopatológica.

AUTORES e ANO	Número de casos avaliados
BHASKAR *et al.*, 1968	20.575
HAPPONEN *et al.*, 1982	15.758
ZANCANARO *et al.*, 1983	4.914
ALMEIDA *et al.*, 1987	1.211
SKINNER *et al.*, 1987	13.378
WEIR *et al.*, 1987	15.783
LAYFIELD *et al.*, 1995	30.056
CHIDZONGA *et al.*, 1996	1.723
TAY *et al.*, 1999	2.057

2.2. PARTE II

TUMORES MALIGNOS

Os tumores malignos que acometem a cavidade oral variam entre 2 a 7% de todos os tipos de câncer. Dentre estes tumores aproximadamente 90% são carcinomas espinocelulares. (BINNIE *et al.*, 1984). No Brasil, o carcinoma espinocelular representa 7% dos casos de câncer em homens e, 1,7% em mulheres. Já nos Estados Unidos este número é de 3% para os homens e de 1,7% para mulheres (INCA, 2001, COTRIM *et al.*, 2001, RIES *et al.*, 2001).

KROLLS *et al.* (1976) realizaram um levantamento de 14.253 casos de carcinomas espinocelulares orais onde o lábio inferior (38%), a língua (22%) e o assoalho bucal (17%) foram os locais mais afetados. Ainda segundo estes autores, cerca de 90% dos tumores malignos da cavidade oral são CECs.

No ano seguinte, ROSSI *et al.*(1977), apresentaram a epidemiologia de 4.793 lesões orais com ênfase nas neoplasias malignas e lesões pré-malignas. O carcinoma espinocelular foi o mais prevalente, representando 1,66% do total e cerca de 74% entre todas as neoplasias malignas analisadas.

KRUTCHKOFF *et al.* (1990) avaliaram 566 casos de tumores malignos do Serviço de Patologia Oral da Universidade de Connecticut. O carcinoma espinocelular foi o mais prevalente (72,53%) seguido dos tumores de glândulas salivares menores (10,99 %).

Os sarcomas são neoplasias que raramente acometem a região de cabeça e pescoço, representando menos de 1% dos tumores malignos desta região (SETZEN *et al.*, 1979). FIGUEIREDO *et al.* (1988) dentro das 10.700 sarcomas presentes nos arquivos do Departamento de Patologia do Hospital A.C.Camargo, em 27 anos de experiência, encontraram apenas 94 sarcomas de tecido mole na região de cabeça e pescoço, sendo o fibrossarcoma o tumor mais freqüente.

NAGLER *et al.* em 2000, mostraram que em 30 anos de experiência em um Hospital israelense, apenas 25 casos de sarcomas na região maxilofacial foram diagnosticados.

BENNETT *et al.* (2000) revisando os arquivos do Departamento de Patologia do Eastman Dental Institute (Londres, Inglaterra) encontraram 25 casos de Osteossarcomas intraorais num período de 30 anos. A idade média foi de 37 anos, notou-se uma pequena predileção pelo sexo feminino e a mandíbula foi o local mais acometido (24 casos). O estudo de TAKAHAMA JR. *et al.* em 2002 analisando 25 casos de osteossarcomas de cabeça e pescoço atendidos no Departamento de Cirurgia de Cabeça e Pescoço e Otorrinolaringologia do Hospital A.C. Camargo de São Paulo verificou que a média de idade foi de 29 anos, com predominância discreta pelo sexo feminino. A mandíbula foi o local mais acometido (60%), seguido pela maxila (36%).

PARACOCCIDIOIDOMICOSE

Paracoccidioidomicose é uma infecção fúngica freqüente em alguns países da América do Sul. O Brasil apresenta áreas endêmicas desta doença, como o Estado de São Paulo. Clinicamente pode ser confundida com o carcinoma espinocelular, sendo necessário a realização de biópsia ou citologia nas lesões bucais para a detecção do *Paracoccidioides brasiliensis* (ALMEIDA *et al.*, 1991). BICALHO *et al.* (2001) analisaram 62 casos de paracoccidioidomicose encaminhados a duas Universidades na cidade de Belo Horizonte num período de 43 anos. 97% dos casos ocorreram no sexo masculino com idade média de 40 anos. Em 30% dos casos as lesões eram múltiplas e as principais localizações foram rebordo alveolar e gengiva.

TUMORES PEDIÁTRICOS

SATO *et al.* (1997) realizaram estudo relativo a tumores pediátricos da cavidade oral e encontraram 250 diagnósticos num período de 28 anos. Desse total, 93% representaram tumores benignos e 7% neoplasias malignas. O hemangioma foi o tumor benigno mais prevalente com 69 casos. Os sarcomas constituíram-se na principal neoplasia maligna e foram relatados 47 casos de odontomas.

Em 1998, CHEN *et al.* mostraram dados epidemiológicos de 534 biópsias realizadas numa população pediátrica do Taiwan, sendo que 27,8% corresponderam a mucocele, 9,65% a cisto dentígero e 7,72% a odontoma. Lesões benignas não odontogênicas corresponderam a 15,6% dos casos, lesões odontogênicas 14,3%, e malignas não odontogênicas a 2,11%.

Em 2000, MAAITA mostrou a incidência de tumores em pacientes com idade abaixo de 18 anos em um período de 18 anos. Esses casos corresponderam a 11% do total do arquivo, onde 91% eram neoplasias benignas e 9% malignas. Hemangioma foi o tumor benigno mais prevalente, sarcomas as neoplasias malignas e o odontoma o tumor odontogênico mais encontrado.

O trabalho de MAIA *et al.* (2000) avaliou 1.018 biópsias orais de pacientes em idade pediátrica, enviadas ao Serviço de Diagnóstico Oral da Universidade Federal de Minas Gerais. As lesões mais prevalentes foram cisto

dentígero, hiperplasia fibrosa, mucocele e lesão periférica de células gigantes. O odontoma foi o tumor odontogênico mais encontrado.

TUMORES ODONTOGÊNICOS

REGEZI *et al.* (1978) analisaram 54.534 biópsias e relataram uma incidência de 1,3% para os tumores odontogênicos. Os odontomas representaram 37% e os ameloblastomas 11%. O tumor odontogênico adenomatóide e os mixomas odontogênicos representaram 3% do total.

Em 1994, DALEY determinou a incidência de tumores odontogênicos, cistos odontogênicos e cistos não-odontogênicos em 40.000 casos do Serviço de Diagnóstico de Patologia Oral da Universidade de Western Ontario, Canadá. Estas três patologias corresponderam a 19,32% dos casos. Dentre os tumores odontogênicos (1,11% do total), os odontomas corresponderam a 51,53% e os ameloblastomas a 13,52%. Dos cistos odontogênicos (17,20% do total), os radiculares corresponderam a 61,15% e dentígero a 24,08%. Dos cistos não odontogênicos (1,01%), o cisto do ducto nasopalatino correspondeu a 73,43% dos casos.

O estudo de ODUKOYA em 1995 revelou a epidemiologia dos tumores odontogênicos numa população nigeriana dentro de um período de 21 anos. 289 casos foram encontrados e 58,5% corresponderam a ameloblastomas, ocorrendo principalmente em homens e em região posterior de mandíbula. Também numa população nigeriana, AROTIBA *et al.* (1997) analisaram 128 tumores odontogênicos por um período de 15 anos. Os resultados mostraram

que o ameloblastoma representou 16% dos casos, mixoma odontogênico 16% e o tumor odontogênico adenomatóide 13%.

MOSQUEDA-TAYLOR *et al.* em 1997 avaliaram 349 casos de tumores odontogênicos encaminhados a quatro centros de diagnóstico na Cidade do México. 98,8% dos casos eram tumores benignos, onde o odontoma (34,6%), ameloblastoma (23,7%) e mixoma (17,7%) foram os mais freqüentes.

LU *et al.* (1998), analisaram 759 casos de tumores odontogênicos na população chinesa em um período de 42 anos. 93,9% dos casos eram benignos, onde o ameloblastoma predominou com 58,6% dos casos. Os odontomas, geralmente descritos como o tumor odontogênico mais prevalente teve uma baixa incidência (6,7%).

TUMORES DE GLÂNDULAS SALIVARES

Quanto aos tumores de glândulas salivares, temos que nos Estados Unidos a incidência anual varia de 0,4 a 6,5 casos por 100.000 indivíduos, representando menos de 3% de todas as neoplasias de cabeça e pescoço (SPIRO, 1986; ELLIS & AUCLAIR, 1996).

A revisão de grandes séries de neoplasias de glândula salivar mostra que de 64% a 80% dos tumores primários de origem epitelial ocorrem em parótida, 7% a 11% em glândula submandibular, menos de 1% em glândula sublingual e de 9% a 23% em glândulas salivares menores. Quanto a sua natureza, de 54 a 79% das neoplasias de glândula salivar são benignas e de 21

a 46% são malignas (ENEROTH, 1971; EVESON & CAWSON, 1985; SEIFERT *et al.*, 1986; SPIRO, 1986; VARGAS *et al.*, 2002).

No estudo realizado com 201 casos de tumores de glândula salivares menores, ISACSSON *et al.* (1983) observaram que o adenoma pleomórfico foi o tumor predominante com 140 casos (70%) seguido pelo carcinoma adenóide cístico com 21 casos (10,4%), adenocarcinomas com 15 casos (7,5%) e carcinoma mucoepidermóide com 13 casos (6,5%).

O trabalho de WALDRON *et al.* em 1988 mostrou que dentre os 426 tumores de glândulas salivares menores, 174 corresponderam a adenomas pleomórficos, 65 carcinomas mucoepidermóides, 47 adenocarcinomas polimorfos de baixo grau, 46 adenomas monomórficos e 40 carcinomas adenóide císticos.

O estudo retrospectivo de 33 anos realizado por LOYOLA *et al.* (1995) mostraram a epidemiologia de 164 casos de tumores de glândulas salivares menores encaminhados ao Laboratório de Patologia Oral da USP-SP., onde, 62% foram classificados como benignos e 38% como malignos. O palato, mucosa jugal e lábios foram os locais mais prevalentes. O adenoma pleomórfico foi o tumor benigno mais prevalente enquanto que o carcinoma mucoepidermóide e o carcinoma adenóide cístico foram os malignos mais encontrados.

Em um estudo com 106 tumores de glândulas salivares menores, NEELY *et al.* (1996) descreveram que dentre os tumores benignos, o adenoma pleomórfico correspondeu a 68% dos casos e o adenoma monomórfico a 10%.

Já dentre os tumores malignos, o carcinoma mucoepidermóide representou 34% e o carcinoma adenóide cístico a 21%. LOPES *et al.* (1999) realizaram um estudo de 196 pacientes com tumores de glândulas salivares menores diagnosticados entre 1954 e 1993 no Hospital A.C.Camargo em São Paulo e verificaram que 128 casos eram malignos e 68 benignos e que 65% dos casos acometeram o palato. Nesta casuística o adenoma pleomórfico foi o tumor benigno mais comum e o carcinoma mucoepidermóide foi o predominante entre os malignos. Ao compararmos os dados dos trabalhos de LOYOLA *et al.* (1995) e LOPES *et al.* (1999), observamos que apesar dos estudos terem sido realizados na mesma década e com a mesma população, os resultados foram antagônicos, mostrando que estudos realizados em ambiente hospitalar, mostram prevalências de tumores malignos superiores aos realizados em centros odontológicos especializados.

INFORMATIZAÇÃO EM SERVIÇOS DE PATOLOGIA ORAL

É indiscutível a necessidade de informatização em todas as áreas e, os trabalhos de GAMBLE & MANDER (1981) e JOSHI *et al.* (1992), realçam a relevância da coleta de dados em Odontologia em sistemas computadorizados para melhorar a qualidade dos dados arquivados. PRIDDY *et al.* (1985) mostraram que a análise de dados de um serviço de biópsia em Patologia Oral pode fornecer informações relevantes ao diagnóstico e tratamento das lesões. Em nosso meio deve-se destacar as atividades do Dr. Moacyr Novelli, que realizou o levantamento epidemiológico do Departamento de Patologia Bucal da Faculdade de Odontologia da Universidade de São Paulo - FOUSP-SP (1978).

3. Proposição

O presente trabalho, composto por dois artigos, teve como objetivo geral avaliar a freqüência de lesões orais submetidas ao Departamento de Diagnóstico Oral da Faculdade de Odontologia de Piracicaba em um período de 32 anos e, traçar um perfil epidemiológico de doenças orais na região de Piracicaba. Os objetivos específicos foram: 1- desenvolver um *software* de banco de dados com a finalidade de agrupar os dados e facilitar a análise da casuística; 2- analisar a freqüência dos 8.875 casos de doenças orais encaminhados ao Serviço de Diagnóstico Oral de FOP/UNICAMP no período analisado; 3- verificar especificamente a freqüência dos Tumores Odontogênicos.

4. Material e Métodos

PARTE I. Desenvolvimento do Programa de Informática

Com o auxílio do Centro de Processamento de Dados da FOP/UNICAMP, um programa de informática em linguagem *Delphi* foi desenvolvido exclusivamente para o armazenamento de informações dos diagnósticos histopatológicos revisados.

A base de dados incluiu o nome do paciente, bem como idade, sexo, localização anatômica e diagnóstico principal. O programa permite uma análise estatística descritiva das lesões, considerando os campos da base de dados.

O sistema inclui um menu principal onde o usuário escolhe a opção desejada, sendo elas: *Banco de Lâminas, Manutenção, Relatórios, Busca, Back-up, Sobre, Troca de Senha, Usuários e Sair.* (Figura 1).

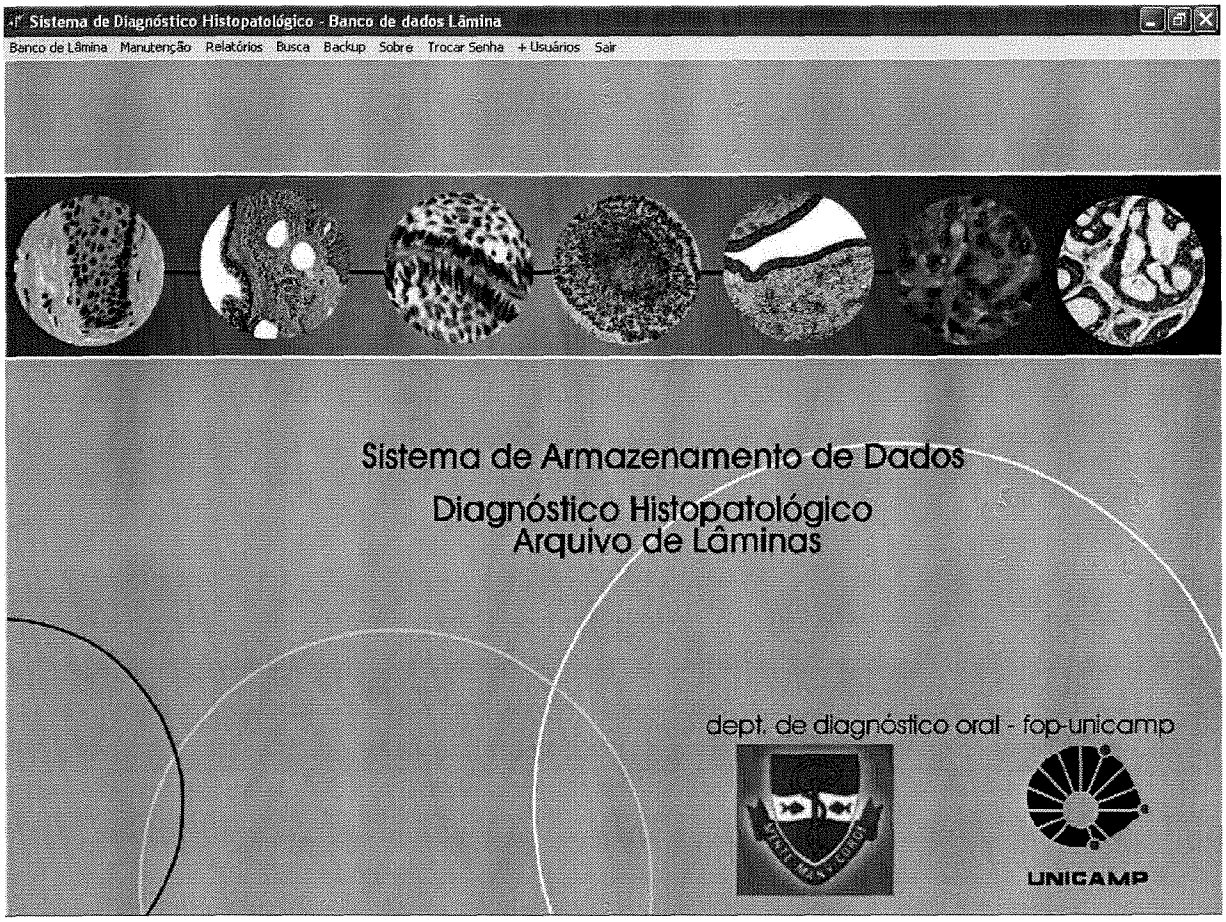

Figura 1. Tela inicial do *software* indicando as opções disponíveis aos usuários.

A opção *Banco de Lâmina* fornece acesso ao sistema de inclusão, alteração ou remoção de dados sendo também possível uma busca rápida pelo Nome do paciente ou Número do caso (Figura 2).

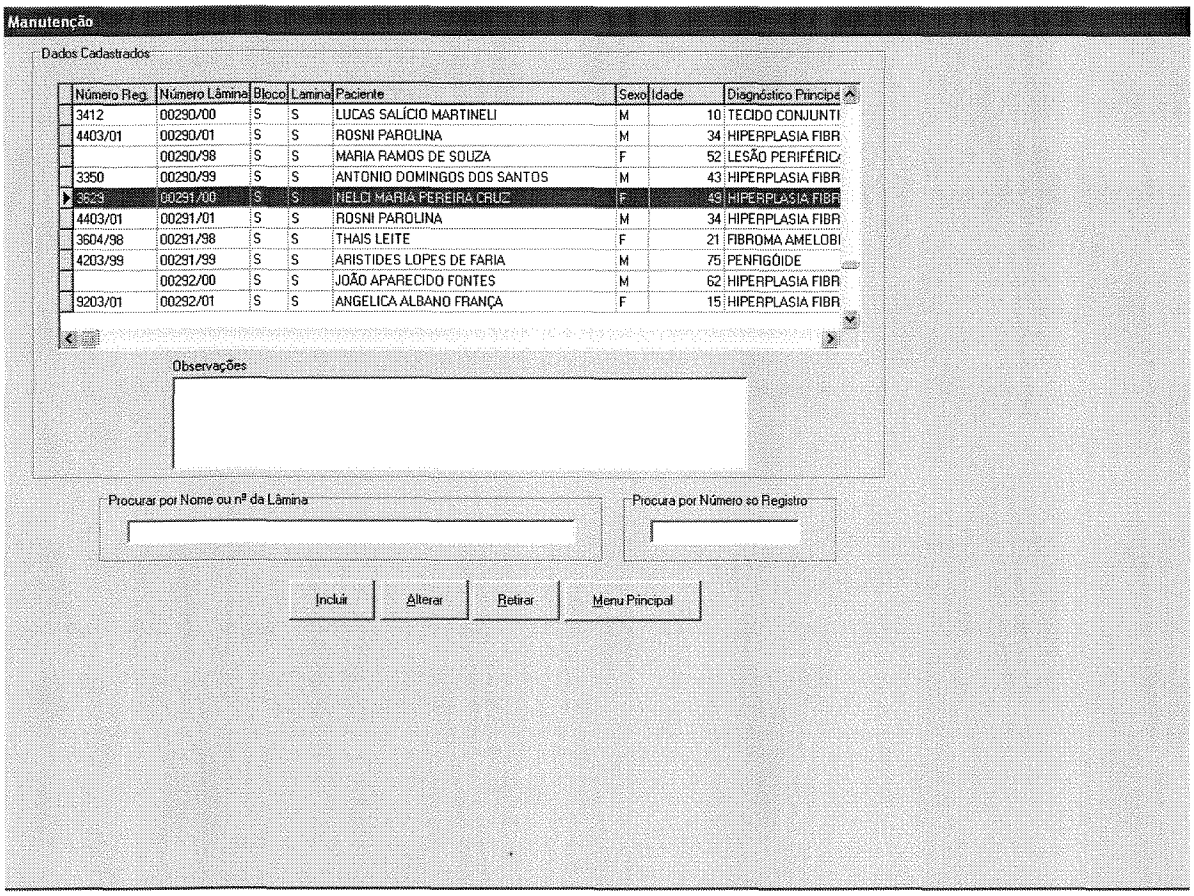

Figura 2. Opção *Banco de Lâminas.*

A opção *Manutenção* inclui a lista de diagnósticos principais e localização anatômica usada na inclusão dos dados. Neste menu, podemos também obter relação total destes diagnósticos e localizações disponíveis (Figura 3).

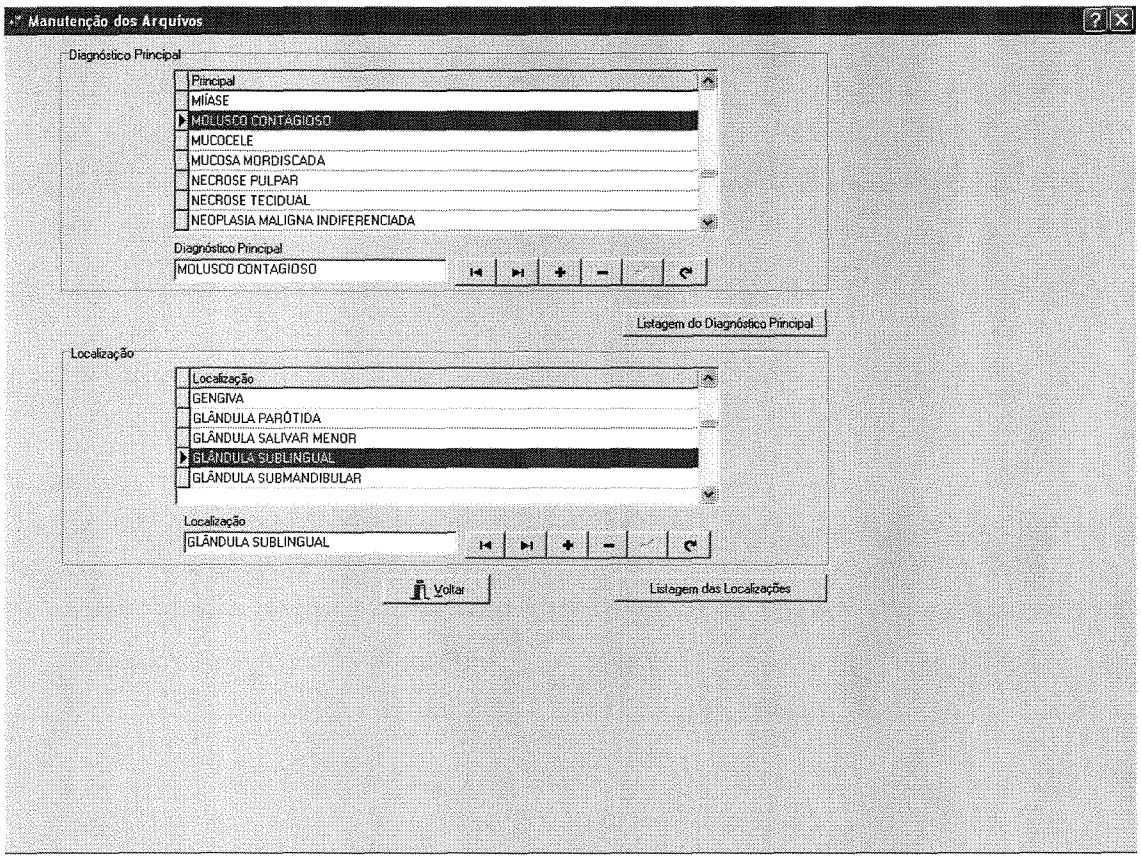

Figura 3. Opção *Manutenção.*

A opção *Relatórios* dá acesso ao usuário à relatórios específicos para controle do acervo, como uma listagem geral ou controle das lâminas e blocos ausentes/presentes; bem como uma listagem anual dos casos diagnosticados. Já a opção *Busca* tem a finalidade de pesquisa no acervo, proporcionando ao usuário facilidade na obtenção das informações desejadas, na qual deve fazer pesquisas restringindo os campos desejados (Figuras 4 e 5).

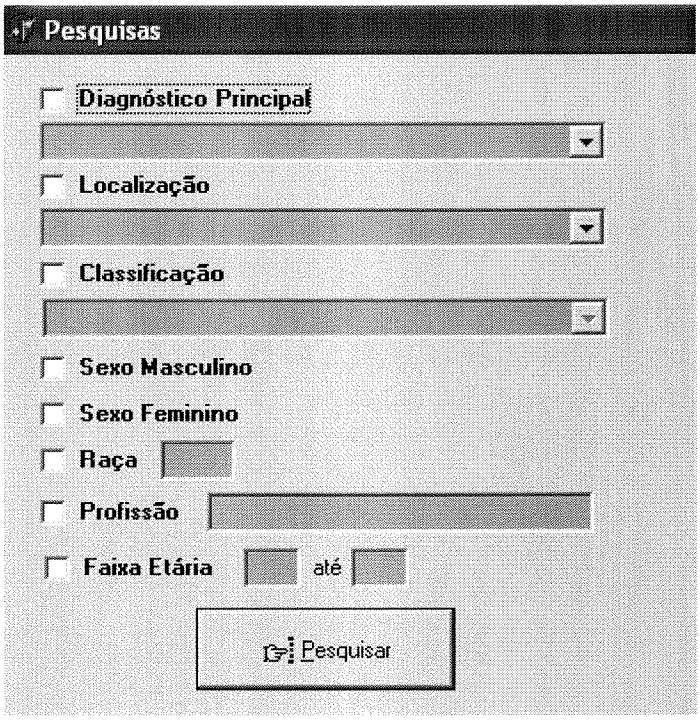

Figura 4. Opção *Busca:* variáveis de escolha disponíveis para o usuário.

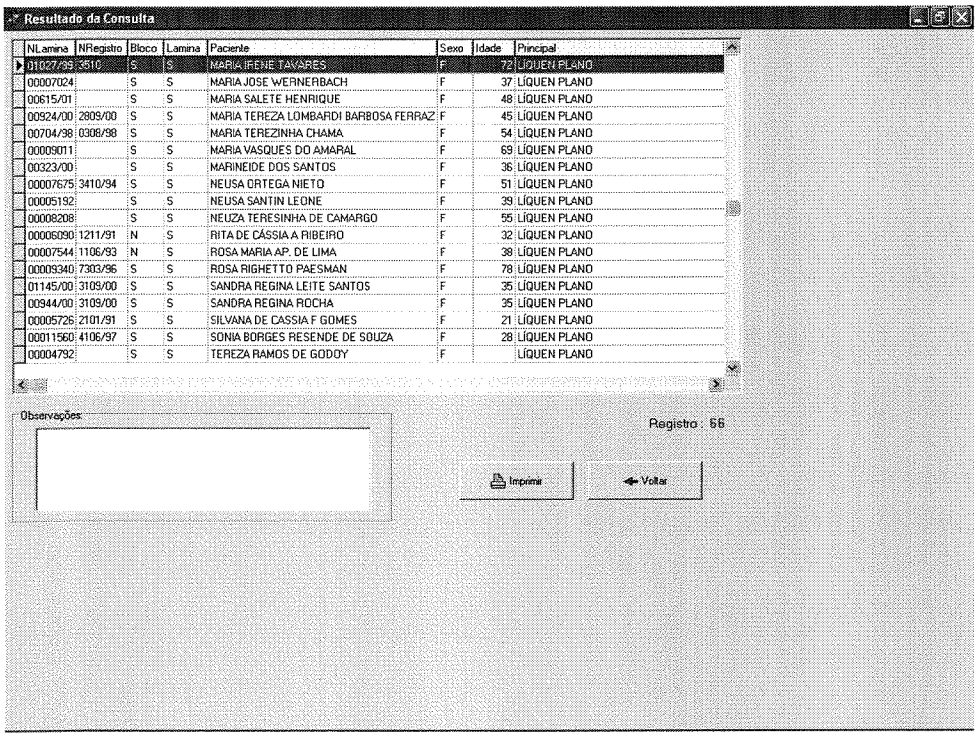

Figura 5. Opção *Busca:* exemplos de resultados em uma pesquisa específica para "Líquen Plano + mucosa jugal + sexo feminino".

PARTE II. Avaliação e revisão dos casos

As lâminas do Arquivo de Lâminas da Disciplina de Patologia Bucal da Faculdade de Odontologia de Piracicaba, referentes ao período entre 1968 a 2000 tiveram seus diagnósticos revisados e reavaliados por dois patologistas orais. O total de casos analisados foi de 8.875. As informações disponíveis foram lançadas no programa de informática descrito anteriormente. Além disso, todos os blocos em parafina foram organizados e checados presença e estado de conservação. Muitos casos precisaram de novas montagens das lâminas, novas colorações e novos cortes, os quais foram, sempre que possível, realizados. Em casos com diagnóstico de neoplasia maligna indiferenciada foram realizadas colorações imunohistoquímicas para tipagem histológica dos tumores.

5. Resultados e Discussão

CAPÍTULO 1 - A Survey of 8,875 Oral and Perioral Biopsies in a Brazilian Population.

Artigo enviado para publicação na revista Community Dentistry and Oral Epidemiology.

CAPÍTULO 2 – Tumores Odontogênicos: Análise de 113 casos da Faculdade de Odontologia de Piracicaba-UNICAMP.

Artigo aceito para publicação na Revista de Pós-Graduação da Faculdade de Odontologia da Universidade de São Paulo.

A SURVEY OF 8,875 ORAL AND PERIORAL BIOPSIES IN A BRAZILIAN POPULATION.

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A survey of 8,875 oral and perioral biopsies in a Brazilian population.

Oral biopsies survey in Brazil

Abstract

OBJECTIVE - The purpose of this study is to show the frequencies of oral and perioral lesions submitted to the Oral Diagnostic Service of the Oral Pathology Department at the School of Dentistry of Piracicaba – UNICAMP during a 32-year period. MATERIALS AND METHODS - Two investigators reviewed each slide and a computerized data base system was used to collect and evaluate the 8,875 cases. RESULTS - The majority of the oral biopsies were taken from either infectious or reactive lesions as Fibrous Hyperplasias (26%), Periapical lesions (11%) and Periodontitis (10%). Squamous Cell Carcinoma was responsible for 5% of the cases corresponding to 86% of all malignant neoplasms. It is interesting to notice the occurrence of 150 cases of Paracoccidioidomycosis. Odontogenic tumours corresponded to 1.2% of the total. CONCLUSION - These results may be helpful for general dental clinicians and contribute for epidemiological figures of oral diseases.

Keywords: Brazil, epidemiology, histopathology, oral lesions

Introduction

Epidemiological studies of oral diseases are important to verify the relative prevalence of reactive, infectious, cystic and neoplastic diseases, and to determine strategies of prevention and treatment. Moreover, geographical differences may lead to clues regarding the causes of these lesions. Frequency of oral diseases varies throughout the world, and it is important to have information not only of countries, but also of each specific region. For example, Brazil has enormous differences among its regions relating to economical, cultural and demographic aspects that may reflect different prevalence of oral lesions. This study was evaluated in a city located at São Paulo State, which is the most developed at this country.

The aim of this study is to show the frequency of 8,875 oral and perioral lesions submitted to the Oral Diagnostic Service of the Oral Pathology Department at the School of Dentistry of Piracicaba – UNICAMP, Brazil during a 32-year period.

Materials and Methods

A total of 8,875 oral and perioral biopsies were submitted to the Department of Oral Pathology of the Dental School of Piracicaba, University of Campinas, State of São Paulo, Brazil from 1968 to 2000. The vast majority of cases were contributed by the local faculty practice and student clinics. Two examiners reviewed all microscopic slides stained with H/E to confirm the diagnosis and proper terminology.

The data was collected and stored in a computer database, using Delphi language. Besides the microscopical diagnosis, the patient age, sex, site of the lesion were entered into the computer program.

Results

All 8,875 cases corresponded to 203 different types of common and rare oral and perioral diseases. The patient's gender was available in 89% of the cases and a slight female predominance was found (53%).

The fifteen most common diagnosed lesions accounted for 83.8% of the total and they are shown on Table 1. Fibrous hyperplasia was the most common lesion, corresponding to 26.8% and the second were periapical lesions with 11.3%.

Oral epithelial dysplasias were found in 85 cases and 42% were diagnosed as mild dysplasia, 29.4% as moderate and 28.3% as severe. Nine cases were diagnosed as Carcinoma *in situ.*

A total of 518 cases (5.83%) were classified as malignant tumors, and of these 447 were squamous cell carcinoma (SCC), corresponding to 86.2% of all types of cancers and 5% of all the material. 80% of SCC affected males, with a mean age was 53.7 years old. Information regarding site of the tumour was available in 356 cases (80%). Floor of the mouth and tongue were the most affected sites, corresponding to 25.8% and 25%, respectively. Lower lip was related to 21.6% of the cases and palate was affected in 6.4%.

The other histological types of cancers found are shown on table 2.

Benign soft tissue tumours were more uncommon than the malignants group. As shown on table 3, a total of 182 cases were diagnosed and Hemangiomas (49.4%) and Lipomas (24.7%) were the most frequent.

Odontogenic tumours were classified according to the World Health Organization (1), and corresponded to 1.2% of the present material. Table 4 shows the different histopathological types, as well as gender and average age distribution.

Paracoccidioidomycosis had a high prevalence, 150 cases, corresponding to 1,7% of the total. Males were affected 90% of the cases, with a peak of incidence on the fifth and sixth decades of life.

Salivary gland tumours corresponded to 73 cases; 63.1% were benign and the histopathological types and gland affected are shown on table 5. Most cases (79.4%) affected minor salivary glands. Parotid gland accounted for 24.5% of the Pleomorphic adenoma. Submandibular gland accounted for 4.5% of the Pleomorphic adenoma, 6.25% of the Mucoepidermoid carcinoma and 25% of the adenoid cystic carcinoma.

Discussion

A computerized database for epidemiological studies of oral diseases has been largely used (2,3). The 15 most common diagnosis presented in this study were similar to those compiled by Bhaskar in 1968 (4) and Weir, Davenport and Skinner in 1987 (5). However these lesions made up more than 80% of the total, which is higher than their results (67.51% and 64.4%, respectively).

As documented by Williams, Hey and Browne in 1997 (6), an increasing number of specimens received in our diagnostic service were observed during this thirty-two years. Historical facts as the improvement in our college in 1988 of the clinical center for diagnosis and surgical treatment of oral diseases must be considered. In 2000 the amount of reported cases were 5.4 times higher than the initial data in 1968. This may also reflect a greater awareness among general clinicians of diseases of the mouth during the last two decades (6).

As expected and already compiled by other authors (4-8) fibrous hyperplasia, periapical lesions (granuloma and cyst), gingivitis and mucoceles were the most common diagnosis and accounted for about 56% of the total.

We considered only the microscopical diagnosis; consequently, a clinical diagnosis of leukoplakia would be included under the histological diagnosis of hyperkeratosis and/or acanthosis, epithelial dysplasia, carcinoma *in situ*, or even squamous cell carcinoma (9). Hyperkeratosis and/or acanthosis were the fifth most common lesion (5.9%), and probably most of them represent leukoplakia.

In our study, 5.83% of all cases were classified as malignant tumours, which is similar to the 5.2% presented by Tay (8) in 1999 in Singapore, but much higher than the values obtained by Weir, Davenport and Skinner (5) in 1987 (2.5%), and Bhaskar (4) in 1968 (1.77%) in USA and by Happonen and Ylipaavalniemi (7) in 1982 (0.5%) in Finland. Squamous cell carcinoma (SCC) is the most common malignant tumour of the oral cavity, corresponding to at least 90% of all oral cancer (10). In the present study, 447 SCC were found, corresponding to 86.2% of the malignant group and 5.0% from the total. Lower frequencies were obtained by other authors (4-5, 7, 11-12). For example, Weir, Davenport and Skinner (5) among 15.783 oral lesions found 256 cases of SCC (1.7% from the total). In Brazil, SCC represent 7% of all cancers in males and 1,7% in females (13) whereas in United States it stands for 3% in males and 1.7% (14).

Hemangioma and Lipoma were the most common benign soft tissue neoplasms. In pediatric oral surveys (15, 16) (1998) hemangioma was considered the most prevalent benign soft tissue tumour.

Lichen planus is a fairly frequent mucocutaneous disease and it made up 2% of our cases. This prevalence is similar to those described by Happonen and Ylipaavalniemi (7) (1.4%) and Weir, Davenport and Skinner (5) (1.7%). Of the 180 patients, 61% were women and 39% men and the average age was about 45 years. According to Eisen (17) recent study of 723 cases of oral lichen planus, 75% were female and 25% male with an average age of the patients higher than

our data. Other important, but rare, mucocutaneous disorders diagnosed were Pemphigus vulgaris (14 cases); Pemphigoid (21 cases), Erythema multiforme (05 cases) and Lupus erythematosus (03 cases).

Paracoccidioidomycosis is an uncommon, progressive systemic mycosis, virtually only seen in Europe and USA in persons who have visited Latin America (18,19). Our survey showed 150 cases, accounting for 1.7% of the total. This high prevalence confirms that Brazil has endemic areas of the disease, as São Paulo State. As reported in other studies (18-20), the majority of the patients were males (90% in our data) with a peak of incidence on the fifth and sixth decades of life. Paracoccidioidomycosis is most relevant to dentistry because lesions may involve especially the head and neck region (18) and should be clinically differentiated from the SCC.

Odontogenic tumours (OT) made up 1,2% of the total cases. The findings of this study are comparable with those of similar investigations (21,22), but inferior to the data obtained by Mosqueda-Taylor *et al* (23) in 1997 (2.5%) and Santos *et al* (24) in 2001 (2.4%). The most common OT was Odontoma, which stands for 40.8%, followed by Ameloblastoma (21.8%), and it is consistent with the data obtained by other authors in America. (21-24). However, odontoma was less frequent in others continents, as documented by Gunham *et al* (25) in Turkey, Wu and Chan (26) in Hong-Kong, Lu *et al* (27) in China and Odukoya (28) in Nigeria with incidence varying from 4,2 to 20% of the total. Interestingly, these same studies also showed that in Asia and Africa, ameloblastomas are the most

common OT, representing e.g. 36,5% of the cases in Turkey and about 60% in China, Hong-Kong and Nigeria. This difference deserves further attention. It is well known that studies based on Medical Hospitals had ameloblastomas as the most common OT besides studies at Dental Colleges shows Odontoma prevalence.

Salivary gland tumours are rare, corresponding to approximately 3% to 10% of neoplasms of the head and neck region (29). It is described a predominance of benign salivary gland tumors (60-to-80%) over malignant tumors (20-to-40%) and table 5 shows that our findings are similar (30-32). Pleomorphic adenoma was the most common tumour (54.8%) in the present study and corresponded to 87% of all benign neoplasms. All epidemiological reports confirm the predominance of pleomorphic adenoma (50 to 80%) among benign and malignant neoplasms of the head and neck (31-33). When we evaluated only salivary malignant tumours, Mucoepidermoid Carcinoma was the most common (59.2%), and it has also been reported to be the most common lesion among salivary gland carcinomas in other series (34-35).

Conclusions

The most common oral lesions analyzed in this survey showed similar results to the reviewed literature. Moreover, this study displayed a high prevalence of Squamous cell carcinoma and Paracoccidioidomycosis.

These results may be helpful for general dental clinicians and contribute for epidemiological figures of oral diseases.

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Tables

Table 1. The 15 most commonly diagnosed oral lesions based on a biopsy survey of 8875 cases in a Brazilian population.

	Diagnosis	*Cases (no.)*	*Cases (%)*
1.	Fibrous hyperplasia	2386	26.8
2.	Periapical cyst and granuloma	1006	11.3
3.	Gingival hyperplasia and chronic gingivitis	889	10.0
4.	Mucocele	718	8.0
5.	Hyperkeratosis and acanthosis	526	5.9
6.	Squamous cell carcinoma	446	5.0
7.	Non-specific chronic inflammation	241	2.7
8.	Papilloma	221	2.4
9.	Pyogenic granuloma	212	2.3
10.	Dental follicle	195	2.1
11.	Lichen planus	180	2.0
12.	Paracoccidioidomycosis	150	1.7
13.	Dentigerous cyst	129	1.4
14.	Non-specific chronic ulceration	106	1.1
15.	Peripheral ossifying fibroma	106	1.1
	TOTAL	**7,115**	**83.8**

Table 2. Malignant neoplasms observed in 8,875 cases of oral lesions analyzed.

Diagnoses	*Cases (no.)*	*Cases (%)*
Squamous cell carcinoma	447	86.2
Non-Hodgkin lymphoma	21	4.0
Mucoepidermoid carcinoma	16	3.1
Polymorphous low grade adenocarcinoma	05	0.9
Langerhans cell histiocytosis	05	0.9
Adenoid cystic carcinoma	04	0.8
Multiple myeloma	03	0.6
Osteosarcoma	03	0.6
Chondrosarcoma	03	0.6
Leiomyosarcoma	02	0.4
Rhabdomyosarcoma	02	0.4
Fibrosarcoma	02	0.4
Metastatic tumours	02	0.4
Liposarcoma	01	0.2
Acinic cell carcinoma	01	0.2
Salivary duct carcinoma	01	0.2
TOTAL	**518**	**100**

Table 3. Benign soft-tissue lesions.

Diagnoses	*Cases (no.)*	*Cases (%)*
Hemangioma	90	49.4
Lipoma	45	24.7
Lymphangioma	16	8.8
Traumatic neuroma	11	6.0
Granular cell tumour	05	2.8
Neurofibroma	05	2.8
Schwannoma	04	2.2
Leiomyoma	03	1.7
Benign fibrous histiocytoma	02	1.0
Solitary fibrous tumour	01	0.6
TOTAL	**182**	**100**

Table 4. Frequency and distribution of 115 odontogenic tumors, considering gender and age.

Histopathological type			Gender				Mean Age (years)
			Female		Male		
	n	*%*	***n***	**%**	***n***	**%**	
Odontoma	47	40.8	26	55.3	21	44.6	24.3
Ameloblastoma	25	21.8	12	48.0	13	52.0	36.8
Odontogenic myxoma	12	10.4	06	50.0	06	50.0	23.3
Calcifying Odontogenic cyst	10	8.7	04	40.0	06	60.0	29.3
Benign cementoblastoma	06	5.2	05	83.3	01	16.6	28.6
Odontogenic fibroma	05	4.3	03	60.0	02	40.0	33.6
Ameloblastic fibro-odontoma	04	3.5	03	75.0	01	25.0	14
Adenomatoid odontogenic tumor	04	3.5	04	100	-	-	12.5
Ameloblastic fibroma	01	0.9	01	100	-	-	21
Malignant ameloblastoma	01	0.9	01	100	-	-	45
Total	**115**	**100**	**65**	**56.5**	**50**	**43.5**	-

Table 5. Frequency of 72 salivary gland tumours diagnosed.

Diagnoses	*Cases (n)*	*Cases (%)*	*Salivary gland affected (n)*	
			Major Glands	Minor Glands
Pleomorphic adenoma	40	54.8	11	29
Mucoepidermoid carcinoma	16	21.9	1	15
Polymorphous low-grade adenocarcinoma	05	6.8	-	5
Adenoid cystic carcinoma	04	5.4	1	3
Canalicular adenoma	02	2.7	-	2
Acinic cell carcinoma	01	1.4	1	-
Salivary duct carcinoma	01	1.4	-	1
Myoepithelioma	01	1.4	-	1
Inverted ductal papilloma	01	1.4	-	1
Warthin's tumour	01	1.4	1	-
Papillary cystadenoma	01	1.4	-	1
Total	**73**	**100**	**15**	**58**

Tumores Odontogênicos: Análise de 113 casos da Faculdade de Odontologia de Piracicaba-UNICAMP.

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Tumores Odontogênicos: Análise de 113 casos da Faculdade de Odontologia de Piracicaba-UNICAMP.

INTRODUÇÃO E OBJETIVOS

Os Tumores Odontogênicos (TO) têm sua origem associada ao órgão dental ou aos seus remanescentes, podendo se desenvolver a partir do epitélio odontogênico, do ectomesênquima ou de ambos.

O comportamento clínico dessas lesões varia consideravelmente. Alguns apresentam potencial de crescimento limitado, provavelmente representando hamartomas, enquanto que outros possuem as características de uma verdadeira neoplasia. Conhecer os aspectos clínicos e epidemiológicos de cada lesão classificada como tumor odontogênico, é de fundamental importância para o seu diagnóstico e tratamento.

Estudos sobre a incidência de tumores odontogênicos ainda são escassos tanto no Brasil como na literatura mundial, porém os trabalhos mostram importantes variações, principalmente quando os estudos são de áreas geográficas diferentes. O objetivo deste trabalho é relatar a incidência dos tumores odontogênicos diagnosticados na Disciplina de Patologia Oral da Faculdade de Odontologia de Piracicaba – UNICAMP e comparar os dados obtidos, com os de outros trabalhos publicados.

MATERIAL E MÉTODOS

Os 113 casos diagnosticados como Tumores Odontogênicos foram provenientes da disciplina de Patologia Oral da Faculdade de Odontologia de Piracicaba da UNICAMP. As lâminas foram coradas com Hematoxilina e Eosina (H&E) e revisadas por dois patologistas orais. As informações clínicas foram obtidas a partir do prontuário do paciente ou da ficha de registro da biópsia. Avaliou-se a localização, a idade e o sexo dos pacientes. Os TO foram classificados histologicamente de acordo com os critérios da Organização Mundial de Saúde (OMS, 1992)[6].

RESULTADOS

De um total de cerca de 9000 casos dos arquivos da Disciplina de Patologia Oral da FOP/UNICAMP, foram diagnosticados 113 TO, correspondendo a 1,26% do total. Foi diagnosticado apenas um caso maligno, correspondendo a um Ameloblastoma Maligno.

O Odontoma foi a lesão mais encontrada, correspondendo a 39,42%. Dentre estes 47 casos, 28 referem-se a Odontoma composto, dos quais 64% localizavam-se na região anterior de maxila. Odontomas complexos representaram 19 casos, com uma distribuição equilibrada tanto na maxila como na mandíbula. O Ameloblastoma com 22,12% (25 casos) foi o segundo tumor mais prevalente. A tabela I mostra a freqüência relativa dos casos analisados.

Considerando-se todos os casos de TO, a freqüência foi ligeiramente maior no sexo feminino (56.63%) e a média de idade entre todos os pacientes foi de 24,6 anos, sendo o mais jovem com 02 e o mais velho 90 anos de idade. Os TO ocorreram predominantemente na 2ª. e 3ª. décadas de vida. Apenas o Ameloblastoma e o Fibroma Odontogênico apresentaram maior incidência na 3ª. e 4ª. décadas. As tabelas II e III correlacionam os tipos histológicos com o sexo e idade dos pacientes. 57,52% dos TO ocorreram na mandíbula, sendo que a região posterior representou 40,70% do total dos casos. A tabela IV mostra a distribuição dos casos de acordo com o local anatômico.

Os Cistos Odontogênicos Calcificantes (COC) foram subclassificados de acordo com Praetorius (1981)[11], sendo que 06 casos corresponderam ao tipo 1A,

ou unicístico simples e 03 casos ao 1B, ou unicístico produtor de Odontoma. Entre os casos unicísticos simples, encontramos um caso de COC periférico. Apenas um caso de Ameloblastoma maligno foi diagnosticado afetando uma mulher com 45 anos de idade, em região anterior de mandíbula que apresentou metástase pulmonar.

DISCUSSÃO

Tumores odontogênicos são lesões pouco freqüentes. Nesta casuística, os TO corresponderam a 1,26% dos casos de patologia bucal diagnosticados na FOP-UNICAMP. Freqüências equivalentes foram encontradas por Regezi *et al.* (1978)[12] e Daley *et al.* (1994)[3], mas inferiores aos dados de Mosqueda-Taylor *et al.*[9] em 1997 que mostraram valores de 2,5% do total dos casos de patologia bucal.

Apesar dos poucos trabalhos sobre a epidemiologia dos TO, há diferenças na incidência principalmente quando são comparados estudos Africanos e Asiáticos com os da América do Norte[1, 3,8,9,10,12,16]. Essas variações na incidência são justificadas por fatores geográficos, étnicos e sócio-econômicos. Deve-se considerar também que dados obtidos junto a centros médicos mostram predominância dos Ameloblastomas[1,4,8,10] , enquanto que em estudos provenientes de Faculdades de Odontologia e clínicas particulares há maior prevalência de odontomas [3,9,12]. Além disso, nota-se que em muitos estudos foram usados diferentes critérios histopatológicos para o diagnóstico dos TO, o que também dificulta a comparação dos resultados.

O tumor mais freqüente nesta casuística foi o Odontoma (39,42%), nos quais 59,57% foram Odontomas compostos e 40,42% Odontomas complexos. Nos EUA, Regezzi *et al.* (1978)[12] encontraram uma prevalência de 67% e Daley *et al.* (1994)[3] de 51,5% em uma população canadense. Em 1997, Mosqueda-Taylor *et al.*[9] em estudo colaborativo mexicano, mostraram ser o Odontoma responsável por

apenas 34,6% dos casos. Nestes trabalhos, o Odontoma composto predominou sobre o Odontoma complexo, sendo responsáveis por 54,7%, 63% e 56,3% dos casos, respectivamente. A incidência dos Odontomas nos trabalhos de Gunham *et al.* (1990) na Turquia[4], Wu and Chan em Hong-Kong (1985)[16], Lu na China (1998)[8] e Odukoya *et al.* na Nigéria (1995)[10] , foi baixa variando entre 4,2 a 20% dos casos. Interessante que estes mesmos estudos mostram que na Ásia e África os Ameloblastomas apresentam alta incidência, sendo responsáveis por cerca 36,5% dos casos na Turquia e cerca de 60% dos casos na China, Hong-Kong e Nigéria. No presente estudo, os ameloblastomas corresponderam a 21,5% dos casos, índice equivalente ao encontrado por Mosqueda-Taylor *et al.* no México[9], mas diferente de Daley *et al.* [3] e Regezi *et al.* [12] que mostraram 13,5% e 11%, respectivamente.

Em relação aos 25 casos de Ameloblastomas diagnosticados, os dados de localização, idade e gênero são semelhantes aos da análise de 3677 casos de Reichart *et al.* [13], ou seja, acometeram na maioria dos casos a região posterior de mandíbula, pacientes com cerca de 36 anos e houve uma leve predileção pelo sexo masculino.

No presente estudo foram diagnosticados 12 casos de Mixoma correspondendo a 10,61% dos TO. Há também grande variação nas taxas epidemiológicas deste tumor em regiões distintas (1,22% em Hong-Kong[16] a 17,7% no México[9]). Diferentemente de outros trabalhos que mostram predominância pelo gênero feminino[1, 4,7,9,12,14], esta casuística mostrou o mesmo número de casos para ambos os sexos, assim como Lu *et al.*[8] A idade média (23,3

anos) é similar a de estudos[1,3,4,8,9,10,12,16]. 75% dos casos acometeram a região posterior de mandíbula, resultado semelhante ao de Regezzi *et al.*[12] e Lo Muzio *et al.* [7], porém Gunham *et al.*[4], Mosqueda-Taylor *et al.*[9] e Lu *et al.*[8] mostraram que tanto a região posterior de maxila como a de mandíbula são acometidas de forma equânime.

Como este trabalho utilizou a classificação da OMS (1992)[6], foram incluídos os casos de Cistos Odontogênicos Calcificantes. Apesar do pequeno número de casos, esta lesão correspondeu a 7,96% (09 casos), sendo este, um índice superior aos de outros trabalhos similares [1,3,4,8,9,12,16]. Todos os casos ocorreram na região anterior da maxila e 66,6% no gênero masculino, diferente de outros estudos que mostraram não haver predileção pela maxila ou mandíbula nesta nem pelo gênero afetado nesta lesão [2,14]. De acordo com a literatura, o COC tem sido associado a Odontomas em 17-26% dos casos [2,14]; e no presente estudo esta associação foi de 33,3%. Encontramos 01 caso de COC periférico, que é considerado raro, com poucos relatos na literatura.

Com relação ao Cementoblastoma Benigno, neste estudo foram diagnosticados 06 casos, correspondendo a 5,30% do total, podendo-se considerar uma taxa elevada quando comparada ao de outros estudos [4,8,9,12]. De acordo com Umansky *et al.*[15] e Jelic *et al.*[5], esta neoplasia representa 1% dos TO. Os aspectos radiográficos e microscópicos são bem característicos, facilitando o diagnóstico. A maioria dos casos (83,3%) afetou o gênero feminino, quando outros trabalhos mostram pequenas diferenças de acometimento quanto ao gênero afetado [5,8,14].

Os tumores odontogênicos malignos representam uma pequena incidência dentre todos os casos. Nosso único caso de Ameloblastoma Maligno representa 0,88% dos casos, com incidência semelhante ao de outras séries[4, 9,12], porém Lu *et al.* (1998)[8] e Odukoya (1995)[10] mostraram taxas de 6,1 e 5,2%.

CONCLUSÃO

Devido a pouca freqüência dos TO, dados epidemiológicos são relevantes para a melhor compreensão dos seus aspectos clínicos e radiográficos. Este estudo mostra a incidência e freqüência dos casos de tumores odontogênicos da região de Piracicaba-SP. Os TO nesta casuística corresponderam a 1,26% de todos os casos diagnosticados em 31 anos. O Odontoma (39,4%) e o Ameloblastoma (23%) foram as duas lesões mais freqüentes. Os TO ocorreram predominantemente entre a 2ª. e 3ª décadas de vida e a região posterior da mandíbula foi o local anatômico mais acometido.

RESUMO

Os tumores odontogênicos (TO) não são freqüentes e poucos trabalhos descrevem casuísticas relativamente grandes. A incidência dos diferentes tipos de TO parece ser variável de região para região, faltando às vezes critérios uniformes de classificação. Num período de cerca de 30 anos foram diagnosticados 113 tumores odontogênicos no Serviço de Patologia Oral da FOP-UNICAMP, correspondendo a 1,26% do total. Todos os casos foram revisados e classificados de acordo com os critérios histológicos da Organização Mundial de Saúde (1992). Odontoma foi a lesão mais comum (39,42%), seguido pelo Ameloblastoma (22,12%), Mixoma (10,61%), Cisto Odontogênico Calcificante (7,96%) e Cementoblastoma Benigno (5,30%). Um caso de Ameloblastoma maligno foi diagnosticado. Esses dados representam os índices epidemiológicos de tumores odontogênicos da região de Piracicaba-SP, e os resultados são comparados com dados da literatura.

ABSTRACT

Epidemiological studies of odontogenic tumors are scarce, and diagnostic criterias are not uniform. The files of the Oral Pathology Department, University of Campinas Dental School were reviewed and all the cases with diagnostic of Odontogenic tumors were retrieved. During a 31-year period (1970-2001), one hundred and thirteen (113) cases were diagnosed as Odontogenic Tumors, corresponding to 1,26% of the total. All cases were reviewed considering the 1992 histologic criteria of the World Health Organization. The most frequent tumors were odontoma (39,42%), ameloblastoma (22,12%), myxoma (10,61%), calcifying odontogenic cyst (7,96%) and benign cementoblastoma (5,30%). These data show the epidemiological rates of odontogenic tumors in a Brazilian population and it is compared with similar works of the literature.

DESCRITORES: tumores odontogênicos, epidemiologia, Brasil.
KEYWORDS: odontogenic tumors, epidemiology, Brazil.

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Tabela I. Freqüência e Distribuição de 113 TO diagnosticados na FOP-UNICAMP.

Diagnóstico Histopatológico	***n***	**%**
Odontoma	47	39,42
Ameloblastoma	25	22,12
Mixoma Odontogênico	12	10,61
Cisto Odontogênico Calcificante	09	7,96
Cementoblastoma Benigno	06	5,30
Fibro-Odontoma Ameloblástico	04	3,53
Fibroma Odontogênico	04	3,53
Tumor Odontogênico Adenomatóide	04	3,53
Fibroma Ameloblástico	01	0,88
Ameloblastoma maligno	01	0,88
Total	**113**	**100**

Tabela II. Distribuição e freqüência de 113 TO de acordo com o gênero afetado.

Diagnóstico Histopatológico	SEXO			
	Feminino		**Masculino**	
	n	**%**	***n***	**%**
Odontoma	26	55.30	21	44.68
Ameloblastoma	12	48.00	13	52.00
Mixoma Odontogênico	06	50.00	06	50.00
Cisto Odontogênico Calcificante	03	33.33	06	66,60
Cementoblastoma Benigno	05	83.33	01	16.67
Fibro-Odontoma Ameloblástico	03	75.00	01	25.00
Fibroma Odontogênico	03	75.00	01	25.00
Tumor Odontogênico Adenomatóide	04	100	-	-
Fibroma Ameloblástico	01	100	-	-
Ameloblastoma maligno	01	100	-	-
Total	**64**	**56.63**	**49**	**43.30**

Tabela III. Distribuição dos casos de TO por faixa etária (média e variação).

Diagnóstico Histopatológico	Idade (anos)	
	Média	Variação
Odontoma Composto (*n*= 28)	19.6	11-42
Odontoma Complexo (*n*= 19)	29.0	09-90
Ameloblastoma (*n* = 25)	36.8	04-70
Mixoma Odontogênico (*n*= 12)	23.3	02-42
Cisto Odontogênico Calcificante (*n*= 09)	27.2	07-49
Cementoblastoma Benigno (*n* = 06)	28.6	08-49
Fibro-Odontoma Ameloblástico (*n*= 04)	14	07-24
Fibroma Odontogênico (*n*=04)	33.6	24-41
Tumor Odontogênico Adenomatóide (n=04)	12.5	11-15
Fibroma Ameloblástico (*n*= 01)	21	-
Ameloblastoma maligno (*n*= 01)	45	-

Tabela IV. Distribuição de acordo com a localização de 113 TO.

Diagnóstico Histopatológico	Localização			
	Maxila		**Mandíbula**	
	Anterior	***Posterior***	***Anterior***	***Posterior***
Odontoma Composto	18	00	06	04
Odontoma Complexo	03	05	07	04
Ameloblastoma	-	02	04	19
Mixoma Odontogênico	-	03	-	09
Cisto Odontogênico Calcificante	09	-	-	-
Cementoblastoma Benigno	-	01	-	05
Fibro-Odontoma Ameloblástico	-	03	-	01
Fibroma Odontogênico	-	01	-	03
Tumor Odontogênico Adenomatóide	02	-	01	01
Fibroma Ameloblástico	-	01	-	-
Ameloblastoma maligno	-	-	01	-
Total	**32**	**16**	**19**	**46**

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Anexos

Outros trabalhos desenvolvidos:

A seguir, são apresentados estudos desenvolvidos durante o curso de Mestrado, a partir das informações fornecidas pela dissertação apresentada.

Calcifying odontogenic cyst: clinicopathological features and immunohistochemical profile of 10 cases

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Abstract

Background: Calcifying odontogenic cyst (COC) is an uncommon odontogenic lesion with few studies describing its immunohistochemical profile and proliferative activity reported in the literature.

Methods: Clinical and histological features and immunohistochemical expression of cytokeratins, Mel-CAM (CD146), bcl-2, PCNA and ki-67, in 10 cases of COC were studied.

Results: All 10 cases affected the maxilla, eight intraosseous and two peripheral. Five central cases were cystic and three were cystic associated with odontoma, and the two extraosseous showed solid histological pattern; immunohistochemistry was positive for cytokeratins 8, 14, 19, AE1/AE3 and 34βE12 and bcl-2 in all cases, and Mel-CAM in six cases. Proliferative activity was greater in the epithelium of central cystic COC in relation to COC associated with odontoma and peripheral lesions.

Conclusion: Calcifying odontogenic cysts showed odontogenic cytokeratin profile and bcl-2 and Mel-CAM expression indicate that these proteins may be involved in the development of COC. There were no recurrences after surgery, irrespective of their proliferative activity.

Key words: calcifying odontogenic cyst; CD146; cytokeratins; ghost cells; immunohistochemistry; Mel-CAM

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Calcifying odontogenic cyst (COC) is an uncommon benign odontogenic lesion that was first distinguished as a separated entity by Gorlin et al. in 1962 (1). Although named and defined as a cyst, there is no agreement in the literature regarding its classification as a cyst or a neoplasm, as some examples of COC show areas suggestive of neoplasia (2). In 1992, the World Health Organization (WHO) classified COC as a neoplasm rather than a cyst, but confirmed that most of the cases are non-neoplastic (3). In view of this duality, many different terminologies have been applied to cystic and solid COC variants, but calcifying odontogenic cyst is the preferred term (4). In addition, several COC classifications have been suggested in the literature, each of them trying to separate its cystic from solid variants, but none has been universally accepted (2, 4–6). However, irrespective

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of its histological pattern and classification as a cyst or neoplasm, prognosis of COC is favorable, with very few recurrences after surgical treatment (7, 8).

Few studies have analyzed the immunohistochemical cytokeratin profile and expression of anti-apoptotic and cellular adhesion molecules in COCs, as well as their proliferative activity. The aim of this work was to evaluate clinical and histological data and to perform an immunohistochemical study of cytokeratins, bcl-2, Mel-CAM (CD146), PCNA, and Ki-67, in 10 cases of COC.

Materials and methods

Ten cases of COC were retrieved from the files of the Oral Pathology Laboratory, School of Dentistry of Piracicaba, State University of Campinas (UNICAMP), Piracicaba, Brazil. Clinical and radiographic data, treatment and follow-up information were obtained from the patients' records. Location of the tumors was considered as incisor, canine, premolar and molar areas, and when the lesion extended for more than one area, the localization of the central part of the lesion was considered as the affected site. All cases were histologically reviewed and classified according to Toida (4). The epithelium lining was divided in basal and suprabasal cells (all cell layers superficial to the basal layer), the last also including ghost cells.

For immunohistochemical reactions, the slides were hydrated and treated with hydrogen peroxide for 30 min to inhibit endogenous peroxidase. Microwave antigen retrieval and overnight incubation with the primary antibodies were performed in all cases (Table 1). For anti-Mel-CAM antibody, no antigen retrieval was necessary. Secondary antibodies conjugated to streptavidin–biotin–peroxidase (Strept ABComplex/HRP Duet, Mouse/Rabbit, Dako A/S, Denmark) were used, followed by diaminobenzidine as the chromogen. Slides were counterstained with Carazz hematoxylin, mounted and analyzed by two of the authors (ERI and FRP). Expressions of the immunohistochemical markers except PCNA and ki-67, was considered as negative or positive i three different areas of all cases: ghost cells, basal and suprabasa epithelial lining cells. For PCNA and ki-67, the percentage o positive cells was calculated after analyzing about 1000 cells in fiv high-power fields of the epithelium lining and solid proliferations

Results

Ten cases of COC were retrieved, representing 8% of all odonto genic tumors of the Oral Pathology Laboratory, School of Den tistry of Piracicaba/UNICAMP. The age of the patients rangec from 7 to 61 years, with a mean of 28.9 years. Six were males anc four females, and Caucasians comprised 70% of the cases. The siz of the lesions was available in eight cases and varied from 1.0 tc 5.0 cm, with an average of 2.5 cm. Swelling in the area, absence o a tooth, and pain were the most common complaints, and time o complaint varied from 2 to 36 months (mean 13.7 months).

All cases affected the maxilla, eight (80%) being intraosseous and two (20%) peripheral (Fig. 1). Five cases (50%) involved the canine area, and only one the molar region (Table 2). Radiographically, out of eight central cases, three were radiolucent and five showed a mixed radiolucent/radiopaque image (Fig. 2). In six cases, the lesions were well-demarcated and in two cases the radiographic margins were irregularly defined. Four cases had an impacted tooth associated with the lesion, a canine in three cases and a supernumerary tooth in one case, and three cases were associated with a complex odontoma.

Clinical and radiographic differential diagnosis included radicular cyst, calcifying odontogenic cyst, residual cyst and odon-

Table 1. Antibodies used for immunohistochemical evaluation of 10 cases of calcifying odontogenic cysts

Antibodies	Clone	Source	Dilution	Antigen retrieval
Anti-cytokeratin 7	OV-TL 12/30	Dako[1]	1:400	Microwave
Anti-cytokeratin 8	35βH11	Dako	1:200	Microwave
Anti-cytokeratin 10	DE-K10	Dako	1:200	Microwave
Anti-cytokeratin 14	LL002	Novocastra[2]	1:200	Microwave
Anti-cytokeratin 18	DC10	Dako	1:400	Microwave
Anti-cytokeratin 19	RCK108	Dako	1:200	Microwave
Anti-cytokeratins	AE1/AE3	Dako	1:200	Microwave
Anti-cytokeratins	34βE12	Dako	1:200	Microwave
Anti-MelCAM	Policlonal	[3]	1:2000	Not necessary
Anti-bcl-2	124	Dako	1:50	Microwave
Anti-PCNA	PC-10	Dako	1:16000	Microwave
Anti-ki-67	MIB-1	Dako	1:200	Microwave

[1]Dako A/S, Denmark; [2]Novocastra Laboratories, UK; [3]Supplied by Dr Ie Ming Shih, Department of Pathology, Johns Hopkins School of Medicine, Baltimore, MD, USA.

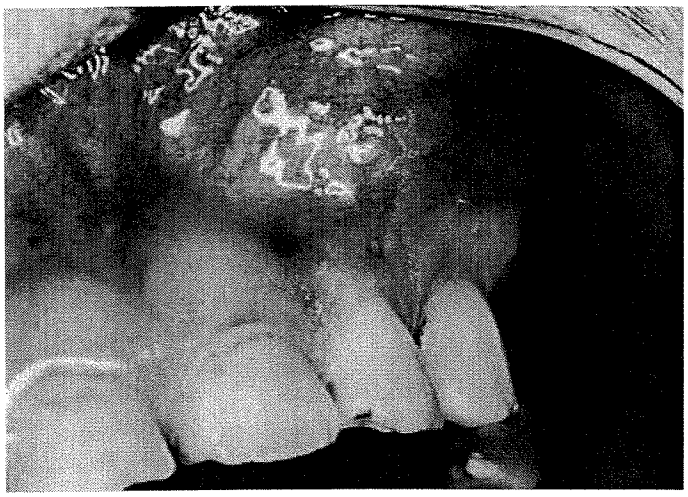

Fig. 1. Calcifying odontogenic cyst. Clinical picture of case 6 showing a large swelling on the left maxillary canine and premolar region of a 49-year-old female.

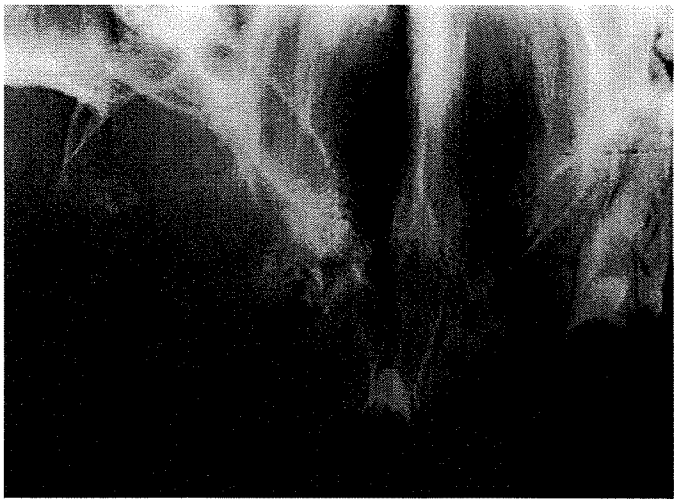

Fig. 2. Calcifying odontogenic cyst. Occlusal radiograph of case 4 showing a well-defined unilocular mixed radiolucent/radiopaque image on the molar/premolar/canine region of the right maxilla of a 43-year-old female.

toma for the intraosseous cases, and nasolabial cyst and neurofibroma for the peripheral cases. All cases were treated by surgical enucleation. Follow-up was available for six cases and varied from 2 to 75 months (mean 26.8 months), and none of the cases have recurred. Table 2 shows the main clinical and radiographic data of the 10 cases of COC.

Histological analysis revealed the typical findings of calcifying odontogenic cyst in all cases, with a stratified epithelial lining composed of basal columnar or cuboidal polarized cells, similar to the reduced enamel epithelium and ghost cells (Fig. 3). The lining epithelium was histologically characterized as non-proliferative in six cases and proliferative in four cases, according to Toida (4). Calcification was found in nine cases and dentinoid material in three cases. Odontoma was associated with three cases and ameloblastomatous proliferation in the capsule was found in one case (Fig. 4). Five central cases were classified as ghost cell calcifying odontogenic cysts, three central cases as ghost cell calcifying odontogenic cysts associated with odontoma and the two peripheral cases were classified as ghost cell calcifying odontogenic tumors, according to Toida (4) (Fig. 5). Table 3 shows a summary of the histological features of 10 cases of COC.

Immunohistochemistry showed that cytokeratins 8, 14, 19, AE1/AE3 and 34βE12 were expressed in the suprabasal cells of all cases and cytokeratins 14 and AE1/AE3 were expressed in basal cells of the epithelium lining of all cases (Fig. 6). Ghost cells expressed only cytokeratins AE1/AE3 and 34βE12. Mel-CAM (CD146) was expressed by the suprabasal cells in six cases, by ghost cells in four cases, and by basal cells in one case (Fig. 7). All cases expressed bcl-2 in the basal and suprabasal cells, but ghost cells were negative in all cases (Fig. 8). Table 4 shows a summary of cytokeratins, Mel-CAM (CD146) and bcl-2 expression in 10 cases of COC.

PCNA expression was positive in eight cases (cases 3–10) and negative in two cases (cases 1 and 2). The mean percentage of

Table 2. Clinical and radiographic data of 10 cases of calcifying odontogenic cyst

Case	Age	Gender	Race[1]	Site	Complaint (months)	Size (cm)	Radiograph	Impacted tooth	Odontoma
1	38	F	C	Canine	12	1.0	No (peripheral)	–	–
2	32	M	C	Premolar	NA	NA	WD[2] Radiolucent	–	–
3	19	M	O	Canine	NA	3.0	WD Mixed	Canine	+
4	43	F	C	Molar	12	5.0	WD Mixed	–	–
5	16	M	C	Canine	NA	NA	WD Mixed	Canine	+
6	49	F	O	Premolar	2	5.0	ND[3] Radiolucent	–	–
7	7	M	C	Incisor	NA	1.0	WD Radiolucent	Supernumerary	–
8	14	M	C	Canine	36	1.0	WD Mixed	Canine	+
9	61	M	O	Canine	8	3.0	ND Mixed	–	–
10	10	F	C	Incisor	12	1.0	No (peripheral)	–	–

[1]C: Caucasian; O: others; [2]Well-defined; [3]Not defined; NA: not available.

Fig. 3. Central calcifying odontogenic cyst. Histopathological view of case 6 showing the epithelial lining composed by a stratified epithelium with basal, suprabasal and numerous ghost cells (H&E, 120×).

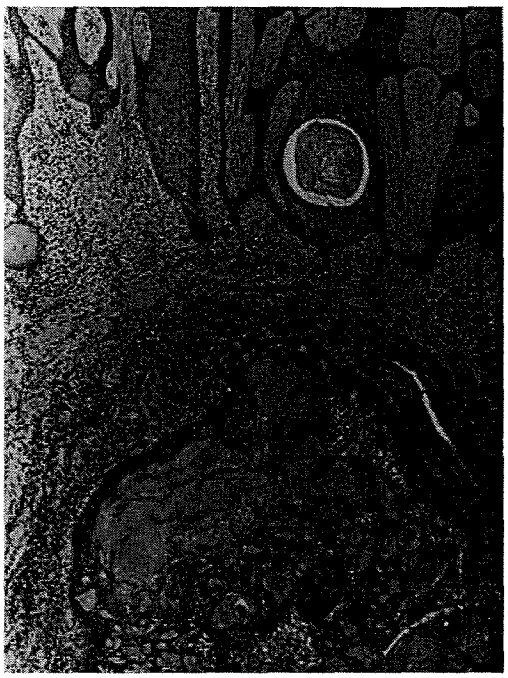

Fig. 5. Peripheral calcifying odontogenic cyst. Histopathological view of case 1 showing a solid peripheral lesion close to the oral cavity epithelial surface lining (H&E, 60×).

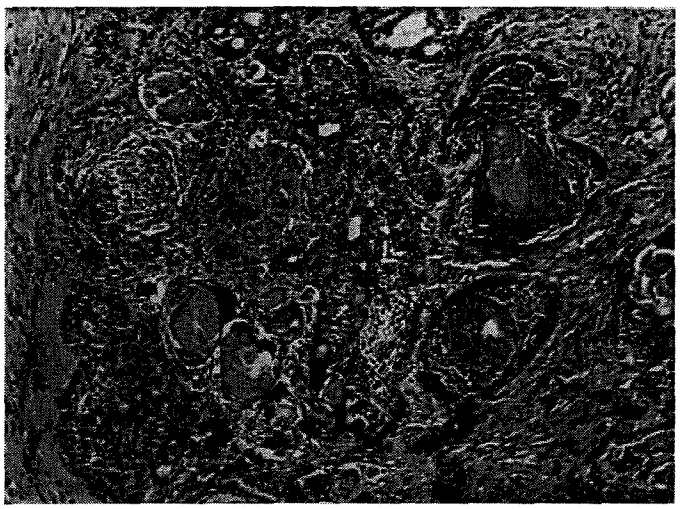

Fig. 4. Central calcifying odontogenic cyst. Histopathological view of case 9 showing ameloblastomatous proliferation in the capsule. (H&E, 100×).

PCNA positive cells was 16% (±7.071 SD), with a range from <1 to 50% of the cells. Ki-67 expression was positive in six cases (cases 4–6, 7, 9 and 10) and negative in four cases (cases 1–3 and 8). The mean percentage of ki-67 positive cells was 1.3% (±0.707 SD), with a range from <1 to 4% of the cells. The highest PCNA and ki-67 proliferative activity was found in case 9, which also showed ameloblastomatous proliferation. PCNA and ki-67 immunohistochemical expression was higher in the proliferative than in the non-proliferative lining epithelium (Table 5). In addition, the proliferative activity of the central cases not associated with odontomas was higher than its value in odontoma-associated and peripheral COCs (Table 5).

Discussion

Since its first description by Gorlin et al. (1), most of the studies on COC describe its clinicopathologic features and histological subclassification. COC represents about 5–7% of all odontogenic tumors and most cases are intraosseous lesions affecting almost equally the maxilla and mandible, with predilection to the anterior segment (incisor/canine area) (2, 5, 7, 9, 10). Peripheral cases are less common, representing 13–35% of the cases (2, 7, 11). It affects mainly adults in the third to fourth decade without gender predilection (2, 7, 8), although Ng & Siar (12) have demonstrated that odontoma-associated COCs predominantly affected younger patients. The most common complaint is an asymptomatic swelling in the area, but pain and teeth dislocation have been uncommonly reported (5, 7, 9). Clinical findings of our cases are

Table 3. Histological features of 10 cases of calcifying odontogenic cysts

Case	Lining epithelium		Dentinoid	Calcification	Odontoma	Ameloblastomatous proliferation	Classification[1]
	Non-proliferative	Proliferative					
1	+	–	–	–	–	–	Peripheral GCCOT
2	+	–	–	+	–	–	GCCOC
3	–	+	+	+	+	–	GCCOC + odontoma
4	–	+	–	+	–	–	GCCOC
5	+	–	–	+	+	–	GCCOC + odontoma
6	–	+	–	+	–	–	GCCOC
7	+	–	–	+	–	–	GCCOC
8	+	–	+	+	+	–	GCCOC + odontoma
9	–	+	–	+	–	+	GCCOC
10	+	–	+	+	–	–	Peripheral GCCOT
Total	6/10	4/10	3/10	9/10	3/10	1/10	

[1]According to Toida (4).

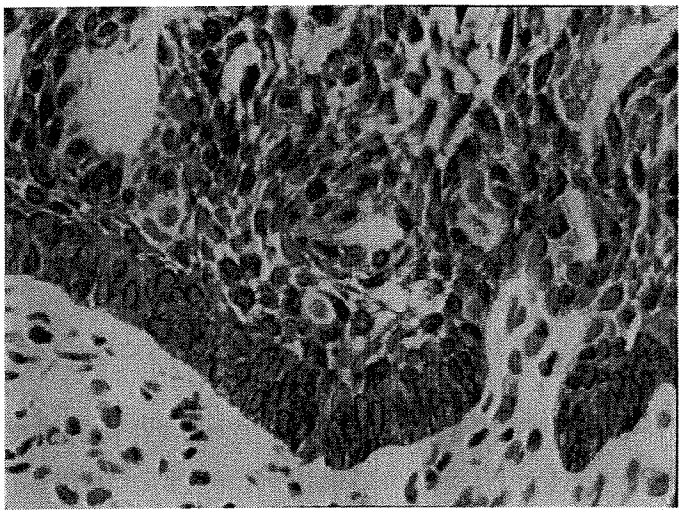

Fig. 6. Immunohistochemical expression of cytokeratin 14 in the basal and suprabasal cells of a central calcifying odontogenic cyst (case 9) (immunoperoxidase, 160×).

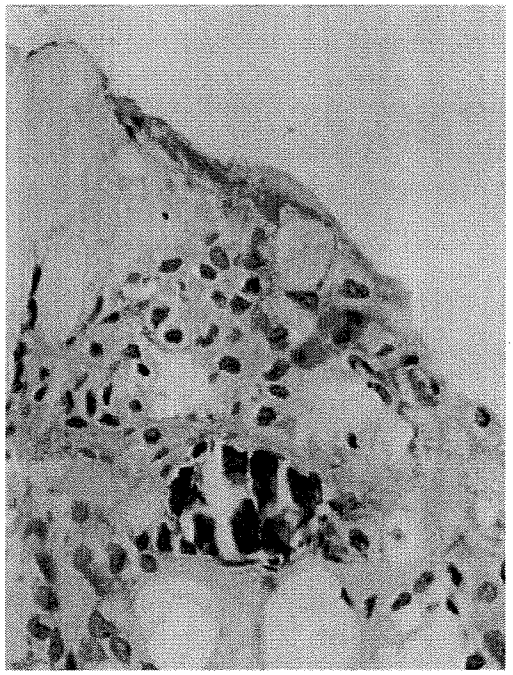

Fig. 7. Immunohistochemical expression of Mel-CAM in the suprabasal and ghost cells of a central calcifying odontogenic cyst (case 6) (immunoperoxidase, 160×).

in agreement with the literature, except that all our cases affected the maxilla. We do not know if it is a simple coincidence or a real racial and geographic predilection.

Radiographically, COC is usually a mixed lesion, a well-defined radiolucency containing some radiopaque foci, features found in 62.5% of our central cases (2, 5, 8, 13, 14). Association with impacted teeth and odontomas is described in 10–32% of the cases, but it was found in 50% of our intraosseous cases (5, 7, 9). None of our cases was submitted to computed tomography, but this technique seems to be useful to detect desquamated keratin in the cystic lumen and peripheral calcifications (14).

Differential diagnosis depends basically on the radiographic appearance of the lesion. Mixed radiolucent/radiopaque lesions are usually interpreted as COC, adenomatoid odontogenic tumor, calcifying odontogenic epithelial tumor or a fibro-osseous lesion (5). However, in cases where the radiographic image is exclusively radiolucent, other differential diagnosis should be included, such as odontogenic cysts (radicular, residual, dentigerous, and keratocyst) or tumors (ameloblastoma, ameloblastic fibroma, and myxoma) (5). In cases predominantly radiopaque, ameloblastic fibro-odontoma, odontomas and fibro-osseous lesions are the main differentials (5). Differential diagnosis of peripheral cases depends on its localization and should include gingival cyst of the adult, mucocele, fibroma, peripheral giant cell lesion, and other benign mesenchymal tumors (like neurofibromas) (11).

Histologically, COC is usually composed of a cystic cavity lined by a stratified epithelium of variable thickness, characterized by a

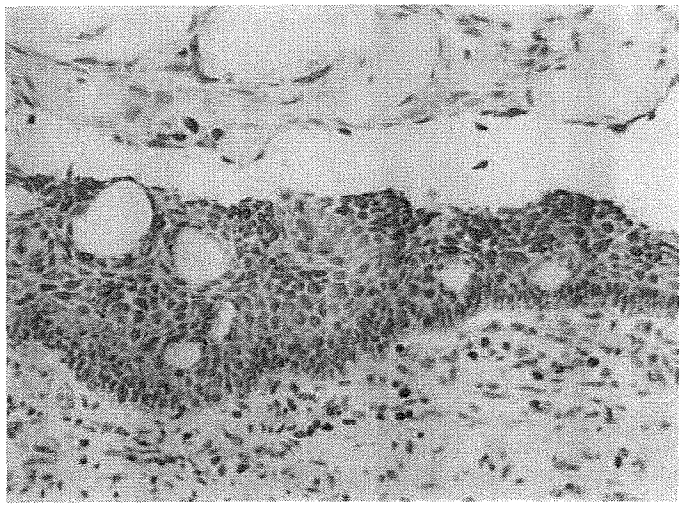

Fig. 8. Immunohistochemical expression of bcl-2 in the basal and suprabasal cells of a central calcifying odontogenic cyst (case 9) (immunoperoxidase, 100×).

Table 4. Immunohistochemical profile of cytokeratins, Mel-CAM and bcl-2 in 10 cases of calcifying odontogenic cysts (number of positive/total cases)

Immunohistochemical markers	Lining epithelial cells		Ghost cells
	Basal cells	Suprabasal cells	
Cytokeratin 7	1/10	8/10	0/10
Cytokeratin 8	9/10	10/10	0/10
Cytokeratin 10	0/10	1/10	0/10
Cytokeratin 14	10/10	10/10	0/10
Cytokeratin 18	1/10	2/10	0/10
Cytokeratin 19	6/10	10/10	0/10
Cytokeratin (AE1/AE3)	10/10	10/10	8/10
Cytokeratin(34βE12)	9/10	10/10	4/10
Mel-CAM	1/10	6/10	4/10
Bcl-2	10/10	10/10	0/10

Table 5. Distribution of PCNA and ki-67 labeling index (mean and range) according to non-proliferative and proliferative lining epithelium and histological typing of 10 calcifying odontogenic cysts

Parameter	PCNA labeling index (mean and range, %)	Ki-67 labeling index (mean and range, %)
Lining epithelium		
Non-proliferative	10 (<1 to 20)	0.7 (<1 to 2)
Proliferative	25(10–50)	2.3 (<1 to 4)
Histological type		
Central GCCOC	20 (<1 to 50)	2 (<1 to 4)
Central GCCOC + odontoma	16.7(10–20)	0.7 (<1 to 2)
Peripheral GCCOT	5 (<1 to 10)	0.5 (<1 to 1)

basal cell layer with hyperchromatic cuboidal to columnar polarized cells resembling mature ameloblasts, and groups of suprabasal cells loosely disposed, similar to the reduced enamel epithelium (1, 9). It has been demonstrated that these lining epithelial cells show ameloblastic differentiation (15). Presence of ghost cells that represent irregularly keratinized epithelial odontogenic cells are highly suggestive of COC (1, 2, 5, 16), although ghost cells can be present in other lesions. The amount and distribution of ghost cells varies from case to case. The lesion is surrounded by a thick connective tissue capsule and inflammation is usually absent, but when ghost cells are in contact with the connective tissue, an inflammatory foreign body reaction is usually present. Dentinoid material can be found adjacent to the epithelial/connective tissue junction. Cytokeratins of the ghost cells can suffer dystrophic calcification, which is also variable from lesion to lesion (7, 17). Odontoma-associated COC seems to show a greater amount of luminal and mural dentinoid substance and also more luminal ghost cells than COCs not associated with odontomas (12).

In addition to these cystic components, the epithelium can show solid luminal and/or mural proliferations, which, in some cases, can have an ameloblastomatous appearance (2). One of our cystic central COCs showed an ameloblastomatous proliferation in the connective tissue capsule, as already described in the literature (18). COC lining epithelium can induce the deposition of dentinoid and some cases can show areas of odontoma formation (8). The COC–odontoma association is the most prevalent one, but some COCs can be also found associated with other odontogenic tumors, like ameloblastomas, adenomatoid odontogenic tumor, and ameloblastic fibroma (5). Although most of the authors believe that odontoma formation is secondary to COC (6, 19), there are some studies that suggest the opposite (2).

Several classifications of COC subtypes have been proposed, but most of them have limitations in separating cystic and neoplastic variants (2, 5, 6). Toida (4) recently suggested a new classification that has included three main subdivisions of COC: cystic, neoplastic, and combined lesions. Although there are also some difficulties in distinguishing cystic COC from the cystic variant of neoplastic COC, this classification seems more practical than the previous ones, so we adopted it in our study. In addition, this classification seems to correlate reasonably with proliferating activity of COC (20, 21). Nevertheless, this considerable histological variation, from typical cystic to solid/neoplastic lesions, brings difficulties in classifying COC as true neoplasms, cysts with neoplastic potential, or even both (4). In summary, there is no consensus in the literature about subtypes and cystic/neoplastic characteristics. It is also difficult to classify the lining epithelium as non-proliferative or proliferative based solely on histological features (2). Immunohistochemical expression of proliferation markers could be a useful strategy to subclassify the lining epithelium proliferation and even to aid distinction of benign and malignant COC variants (8, 20). Our results showed

that, in addition to conventional H&E staining features, PCNA and ki-67 immunohistochemical expression in non-proliferative and proliferative lining epithelium could be useful in establishing diagnostic criteria (8, 20). We found a correlation of both mean PCNA and ki-67 labeling indexes with the epithelial proliferation diagnosed in H&E, supporting its usefulness.

Cytokeratin expression in COC is frequently demonstrated in cells of the epithelium lining, but it is controversial in the ghost cells (2, 17, 22). This antigenic alteration is probably due to coagulative necrosis of the odontogenic epithelium in COC (2). Expression of high- and low-molecular weight cytokeratins in the epithelium lining of COC and its weak positivity or negativity in ghost cells suggest that COC is an aberrant counterpart of the normal dental development (7, 17, 19, 22). Cytokeratin 19 is expressed in all odontogenic epithelia from dental germs in development and in some odontogenic tumors, including COC (8, 23, 24) and, as expected, was expressed in our 10 cases. It has also been demonstrated that cytokeratin 14 is expressed in the inner enamel epithelium in early and late stages of odontogenesis (24) and in odontogenic tumors (23), and this cytokeratin was also expressed in all our cases. Cytokeratin 7 is expressed in remnants of the dental lamina, outer enamel epithelium, and stellate reticulum, as well as in odontogenic cysts, and was expressed in the suprabasal cells of 80% of our cases (23, 24). In contrast, cytokeratin 8 has not been regularly expressed in odontogenic epithelium (24), but it was expressed in all our cases, and probably represents a late change in cytokeratin profile in COCs. Our peripheral and central cases showed similar cytokeratin profile, confirming they are similar odontogenic lesions.

Mel-CAM (CD146 or MUC18) is a 113-kDa heterophilic cell–cell adhesion transmembrane glycoprotein belonging to the immunoglobulin supergene family, whose expression has been described in many normal embryonic and adult tissues (25). This protein has been related to focal adhesion, cytoskeletal organization, intercellular interactions, maintenance of the cell shape, and cellular migration and proliferation control (25). Mel-CAM was frequently expressed in suprabasal and ghost cells in our cases, but it was practically absent in basal lining cells. We did not find any previous description of Mel-CAM expression in odontogenesis or odontogenic lesions to compare with these findings, but our results suggest that this protein can be an important molecule in cellular odontogenic interactions in COC. The expression of Mel-CAM in suprabasal and ghost cells and its absence in basal cells suggest that Mel-CAM can be a marker for differentiation and can be involved in ghost cell formation in COC.

Bcl-2 is an anti-apoptotic protein that has been demonstrated in the epithelial components of tooth germs and in epithelium lining cells of COC (8, 26). This protein was expressed in all our cases, supporting the view that it might have an important role in maintaining viable cells in the COC epithelium lining, and possibly leading to ghost cell formation. However, it was absent in the ghost cells, possibly due to late inactivation or functional structural modifications.

Calcifying odontogenic cysts are treated by conservative surgery, and recurrences are extremely uncommon (5, 7, 8). There is some concern in the literature regarding the influence of proliferative lining epithelium and ameloblastomatous proliferation and prognosis of COC; however, there is still no clear evidence that these features can indicate a less favourable prognosis (7). Our results also showed that central COC cases not associated with odontomas displayed higher proliferative activity than odontoma-associated and peripheral cases. However, all cases had a good prognosis without recurrence.

In summary, COCs are uncommon odontogenic lesions that usually affect the anterior portion of the maxilla and mandible of young adults. About 65–90% of the cases are intraosseous, showing a well-defined radiolucent area containing some foci of calcification. Cytokeratin expression in COCs confirms its odontogenic origin and bcl-2 and Mel-CAM (CD146) molecules seem to participate in COC development. Although peripheral COC, central COC and odontoma-associated central COC can show different proliferative activities, this is not reflected in alterations in treatment and prognosis of these lesions.

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Clinical Report
Oral Pathology

Lipomas of the oral cavity: clinical findings, histological classification and proliferative activity of 46 cases

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Abstract. Lipomas represent about 1 to 5% of all neoplasms of the oral cavity. Although relatively common, few large series of intraoral lipomas and its variants are seen in the literature. Therefore, the authors present the clinical, histological and immunohistochemical features of 46 cases of intraoral lipomas reviewed from the files of the University of Campinas Dental School from 1970 to 2001. Most of the cases affected adults, without gender predilection, and the main involved sites were the buccal mucosa (21 cases), tongue (six cases), lips (six cases) and floor of mouth (five cases). The histological analysis revealed 21 cases of lipoma, 18 fibrolipomas, four intramuscular lipomas, two minor salivary gland lipomas and one spindle cell lipoma. PCNA and ki-67 expression indexes were higher in spindle cell lipoma, intramuscular lipomas and fibrolipomas compared to common lipomas, but the differences were not statistically significant. All lesions were removed surgically and none showed recurrence, regardless of the various proliferative activities.

Key words: lipoma; oral mucosa; proliferating cell nuclear antigen; ki-67 antigen; spindle cell lipoma; sialolipoma; intramuscular lipoma.

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Introduction

Lipomas are the most common soft tissue mesenchymal neoplasms, with 15 to 20% of the cases involving the head and neck region and 1 to 4% affecting the oral cavity[2,5,11,13]. They represent 0.1 to 5% of all benign tumours of the mouth, and are usually found as long-standing soft nodular asymptomatic swellings covered by normal mucosa. Oral lipomas affect predominantly the buccal mucosa, floor of mouth, tongue and lips[2,5,16]. Histologically they can be classified as simple lipomas or its variants, such as fibrolipomas, spindle cell lipomas, intramuscular or infiltrating lipomas, angiolipomas, salivary gland lipomas, pleomorphic lipomas, myxoid lipomas, and atypical lipomas[12].

Although relatively common in the oral cavity, there are few large series of intraoral lipomas in the English-language literature. This paper analysed the clinicopathological features and proliferative activity of 46 oral lipomas.

Material and methods

The files of the Oral Pathology Department, University of Campinas Dental School, were reviewed from 1970 to 2001 and all cases with the diagnosis of lipoma of the oral cavity were retrieved. Information regarding gender and age of the patients, site, size and duration before treatment of the lesions, treatment and length of follow-up were obtained from the patients records.

All haematoxylin-eosin stained slides were reviewed and classified as proposed by Gnepp[5] and Weiss & Goldblum[16], and included lipoma, fibrolipoma, intramuscular and intermuscular lipoma, angiolipoma, angiomyolipoma, myolipoma, myelolipoma,

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benign lipoblastoma, chondroid lipoma, spindle cell lipoma, pleomorphic lipoma and salivary gland lipoma. To confirm the diagnosis of spindle cell lipoma in one case, toluidine blue staining and immunohistochemical reactions were performed with antibodies against S-100 (Sigma, St Louis, USA, dilution 1:10.000), CD34 (Clone QBEND10, Novocastra, UK, dilution 1:600), human muscle actin (Clone HHF35, Dako A/S, Denmark, dilution 1:800) and vimentin (Clone Vim 3B4, Dako A/S, Denmark, dilution 1:400). Immunohistochemistry was also performed in all cases to analyse the proliferative activity, using antibodies against the proliferating cell nuclear antigen (PCNA, Clone PC10, Dako A/S, Denmark, dilution 1:16.000) and ki-67 antigen (Clone ki-S5, Dako A/S, Glostrup, Denmark, dilution 1:200), microwave antigen retrieval and a streptavidin-biotin-peroxidase method (Strept ABComplex/HRP Duet, Mouse/Rabbit, Dako A/S, Denmark). The immunohistochemical PCNA and ki-67 slides were analysed by calculating the average percentage of positive cells in ten high-power fields for each marker in all the cases. Wilcoxon test was applied to compare the mean general ki-67 and PCNA immunohistochemical expression values and also to compare the mean values of each proliferation marker among the histological variants.

Results

During the 31-year period comprising from 1970 to 2001, 46 cases diagnosed as lipomas of the oral cavity were found, representing 0.5% of all lesions of the Oral Pathology Department, University of Campinas Dental School. The mean age of the patients was 52 years, ranging from eight to 80 years, and females represented 57.8% of the patients. The mean reported duration of the lesions was 75.8 months with a range from 15 days to 30 years. The most common site was the buccal mucosa (45.7%), followed by the tongue (13%), lips (13%) and floor of mouth (10.9%) (Fig. 1). The size of the lesions varied from 0.3 to 5.0 cm, with an average of 2.0 cm.

Histologically, lipomas comprised 21 cases (45.7%), followed by 18 cases of fibrolipomas (39.1%) (Fig. 2), four cases of intramuscular lipomas (8.6%), two cases of minor salivary gland lipomas (4.4%) (Figs 3 and 4) and one case of spindle cell lipoma (2.2%) (Fig. 5) (Table 1). In one case diagnosed as spindle cell lipoma, toluidine blue staining showed abundant mast cells interspersed by the spindle cells. Immunohistochemical analysis showed positivity for vimentin and CD34 protein and negativity for S-100 protein and human muscle actin in the spindle cells.

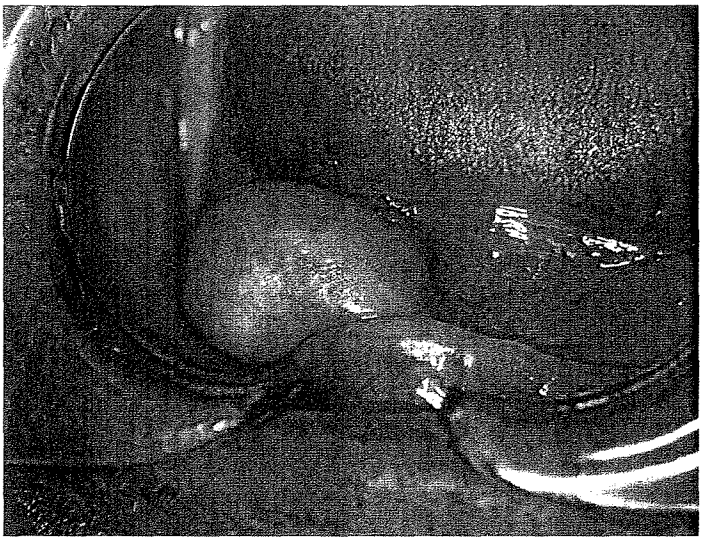

Fig. 1. A pedunculated soft yellowish nodular lesion covered by normal mucosa on the floor of mouth in a 54-year-old woman diagnosed as lipoma.

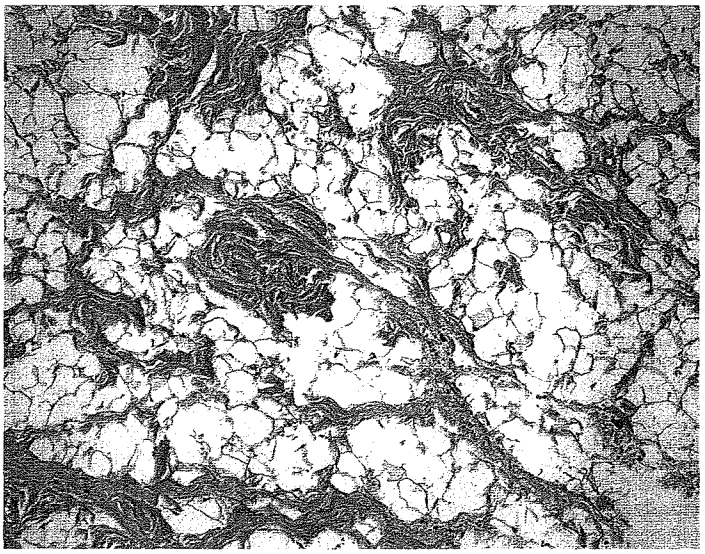

Fig. 2. Microscopical features of fibrolipoma showing mature adipose tissue interspersed by broad bands or fascicles of dense connective tissue (H&E, 200 ×).

The mean percentage of immunohistochemical PCNA expression in all the cases studied was 13.2% (ranging from <1% to 52%), and for ki-67 was 2.8% (ranging from <1% to 16%). The distribution of PCNA and ki-67 expression by different histological groups is shown

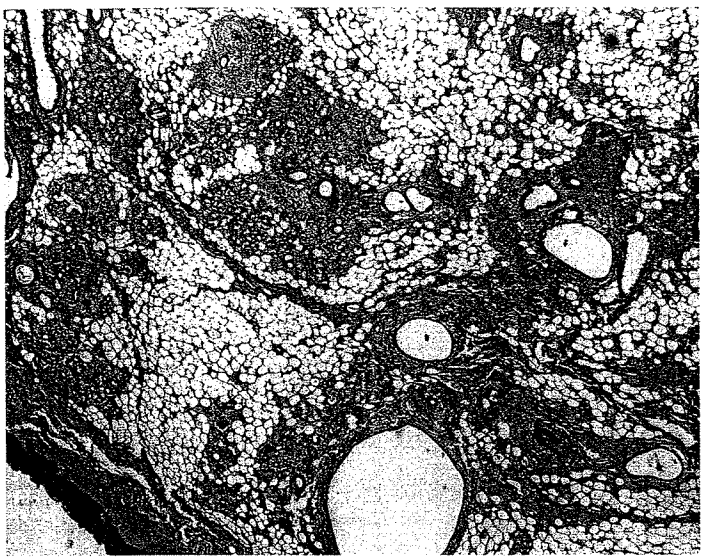

Fig. 3. Minor salivary gland lipoma displaying adipose tissue closely packed with glandular components, surrounded by a thin layer of fibrous tissue and surface stratified squamous epithelium (H&E, 40 ×).

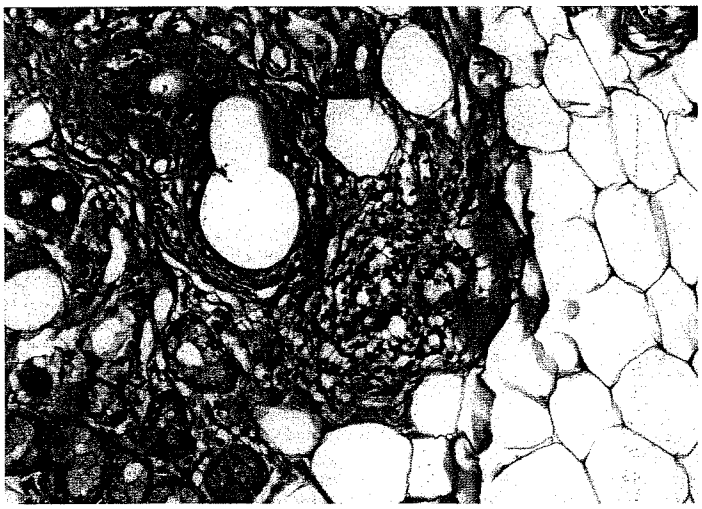

Fig. 4. Higher power view of minor salivary gland lipoma, presenting adipose tissue and salivary glands with atrophic acini and dilated ducts (H&E, 160 ×).

in Table 2. The difference in the mean immunohistochemical expression between ki-67 and PCNA comparing all cases was statistically significant ($P<0.009$). Although there were differences in the mean PCNA and ki-67 indexes among each of the histological variants, none showed statistically significant results.

All cases were treated by surgical approach and after actively reviewing all patients, follow-up information was available for 35 cases (76.1%). None of these cases have recurred after a mean follow-up period of 26.5 months, ranging from 1 to 108 months.

Discussion

Intraoral lipomas usually manifest as long-lasting sessile round to ovoid submucosal nodules affecting the buccal mucosa, buccal sulcus, retromolar area and floor of mouth of adults, as shown by our results[3,7,8,11,13,15]. The great majority of our 46 cases was diagnosed as lipomas (21 cases—45.7%) and fibrolipomas (18 cases—39.1%). Some authors have also reported similar incidences of lipomas and fibrolipomas[6,8,11], although others found that the great majority of cases are lipomas[2,4,7,12,13]. These differences could be explained by real racial and geographic characteristics or simply by different diagnostic criteria. We diagnosed fibrolipomas in cases where the mature adipose tissue was interspersed by broad bands or fascicles of dense connective tissue without presence of capsule. It has been suggested that oral lipomas are more common in males, while oral fibrolipomas are more frequent in females, in contrast with the whole body where lipomas are twice as common in females as in males[2,7]. However, there is no convincing explanation for it in the literature. We could not confirm these differences, as our cases showed a relationship of affected males/females of 1:1.5 for lipomas and of 1:1 for fibrolipomas. Lipomas and fibrolipomas are both usually well-circumscribed and thinly encapsulated, features that help in their differential diagnosis with herniated adipose tissue and fibrous polyp with fat entrapment, respectively[5,16].

Two of our cases were classified as intraglandular lipomas containing atrophic salivary gland acini and dilated salivary gland ducts. NAGAO et al.[9] reported seven cases of a new variant of salivary gland lipoma, called sialolipoma, two of them affecting the palate, with histological findings very similar to our two intraglandular lipomas. As proposed by them, lipomas growing close to salivary glands can induce marked changes in the acini and ductal structures leading to the alterations seen in Nagao's seven cases and in our two cases.

Spindle cell lipoma is an uncommon variant of lipoma first recognized by ENZINGER & HARVEY in 1975[3] that typically occurs in the posterior neck and back regions of adult and elderly men. The histological features of spindle cells,

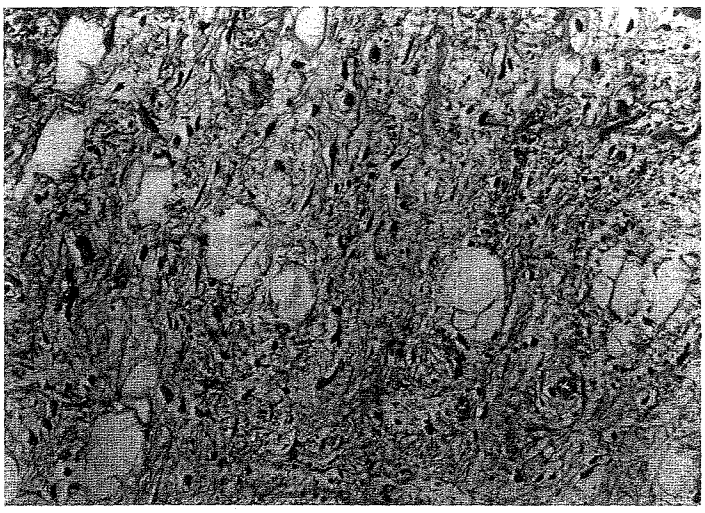

Fig. 5. Spindle cell lipoma showing fibrous and myxoid tissue containing spindle cells and scattered adipocytes (H&E, 160 ×).

Table 1. Distribution of 46 intraoral lipomas according to the site of occurrence and histological classification

	Histological classification					
Site	Lipomas	Fibrolipomas	Intramuscular lipomas	Minor salivary gland lipomas	Spindle cell lipoma	Total
Buccal mucosa	10	10	1	—	—	21 (45.7%)
Tongue	2	1	2	1	—	6 (13%)
Lips	3	2	—	—	1	6 (13%)
Floor of mouth	2	2	1	—	—	5 (10.9%)
Buccal sulcus	1	2	—	1	—	4 (8.6%)
Retromolar area	1	1	—	—	—	2 (4.4%)
Unknown	2	—	—	—	—	2 (4.4%)
Total	21 (45.7%)	18 (39.1%)	4 (8.6%)	2 (4.4%)	1 (2.2%)	46 (100%)

Table 2. Expression of PCNA and ki-67 according to the histological classification of 41 intraoral lipomas*

Histological classification	% of PCNA expression (median and range)	% of ki-67 expression (median and range)	*P*
Lipomas (n=19)	9.5% (<1% to 35%)	1.7% (<1% to 10%)	
Fibrolipomas (n=15)	17.3% (<1% to 52%)	4.8% (<1% to 16%)	
Intramuscular lipomas (n=4)	10.8% (3% to 24%)	1.7% (<1% to 7%)	
Minor salivary gland lipomas (n=2)	15% (<1% to 30%)	<1%	
Spindle cell lipoma (n=1)	40%	<1%	
Total (n=41)	13.2% (<1% to 52%)	2.8% (<1% to 16%)	<0.009

*Paraffin blocks were not available in two cases of lipomas and three cases of fibrolipomas.

mature adipose tissue, collagen bundles and myxoid intersticial matrix, associated to evidentiation of numerous mast cells and immunohistochemical expression of CD34 and vimentin in the spindle cells confirmed the diagnosis of spindle cell lipoma in our case[1,3,10,12,14]. This seems to be the fourteenth case of intraoral spindle cell lipoma reported in the English-language literature, and the first affecting the lip[1,10,12]. In the other 13 cases, the male:female ratio was 1.2:1, the mean age was 55.6 years (ranging from 23 to 75 years) and the affected sites included tongue (five cases), buccal mucosa (four cases), floor of mouth (two cases), palate (one case) and buccal sulcus (one case)[1,10,12].

Intramuscular or infiltrative lipomas are slow-growing painless lesions usually found in the great muscles of the extremities of adult males, histologically characterized by infiltrating adipose tissue and muscle atrophy[16]. Lesions outside the oral cavity could show greater recurrence rates after surgical excision, but intraoral intramuscular lipomas, although not well-limited, rarely show recurrence if completely excised[4,16]. Four of our cases were diagnosed as intramuscular lipomas, but showed no recurrence after surgical treatment. In addition, the proliferative rates were similar to common lipomas. As shown by EPIVATIANOS et al.[4] and two of our cases, intramuscular lipomas have a slight predilection for the tongue, due to the close relationship between the adipose tissue and the muscular layer. Infiltrative lipomas could suggest a false diagnosis of liposarcoma but, as we found in our cases, absence of cellular pleomorphism and nuclear hyperchromatism, and low mitotic activity, supported the diagnosis of intramuscular lipomas. Nevertheless, there is no accordance in the literature if intraoral intramuscular lipomas do really exist or if they represent lipomas with entrapped muscle fibres.

Regarding the proliferative activity of lipomas, we found differences in PCNA and ki-67 expression in the different histological groups of our cases. The proliferative rate of fibrolipomas was greater than common lipomas, but no differences in clinical behaviour were noticed after surgical treatment. Although the increased PCNA expression would suggest faster growing of the lesion, this was not reflected in a worst prognosis, as showed by the absence of recurrence in all the followed-up cases after surgical approach. Phenotypical individual alterations could lead to different proliferative rate expression in the various groups analysed, without reflections in the prognostic features. However, some cases showed short follow-up period, bringing difficulties in the correlation of the proliferative activity with the absence of recurrence. In addition, the limited number of cases in some uncommon histological subtypes prevents more meaningful correlations. We could not find any other report in the English-language literature that analysed the proliferative activity of lipomas to compare our findings, so we suggest that more studies should be encouraged

regarding proliferative activity of lipomas and its histological variants.

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Letter to the Editor

Odontomas and ameloblastomas: variable prevalences around the world?

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Dear Editor,

We collected the epidemiological data of odontogenic tumours from two Brazilian Institutions, a Dental and a Medical Hospital, both in the state of São Paulo. In the Dental Hospital, out of 113 cases, odontomas and ameloblastomas corresponded to 39.4 and 22.12% of the odontogenic tumours, respectively. On the other hand, in the Medical Hospital out of 75 cases, 60% were ameloblastomas, and only 5.3% were diagnosed as odontomas. For obvious reasons, the data from the Medical Hospital have bias. It must be considered that in many countries ameloblastomas are usually diagnosed in dental school, but treatment is performed in a medical hospital. This is not the case for odontomas. This probably is evident for most of us, but the literature is controversial. Nevertheless, some comparative studies considering dental and medical institutions helps to clarify the matter [1,2]. According to Mosqueda-Taylor et al. [2] in a retrospective study of 349 odontogenic tumours in Mexico, including Dental and Medical Hospitals, no odontomas were treated in the last.

When the literature considers these epidemiological variations, the explanation lies on possible ethnic and/or geographical differences [3–6]. It is also common to suggest that ameloblastomas are more common in blacks than in Caucasians [1,3–5,7,8]. This also deserves better consideration. In our view, the reasons for differences in prevalence of odontomas and ameloblastomas are simpler. Table 1 shows some epidemiological data of odontogenic tumours around the world. Based on the original articles, we understood that the data showing a higher prevalence of ameloblastomas over odontomas were obtained from Medical Hospitals.

Odontomas frequently are found in routine panoramic X-ray performed by dentists. Most cases are treated by a dentist at their office or in a dental school, without previous biopsy. In several developing countries many cases are not registered or sent for histological con-

Table 1
Percentage of odontomas and ameloblastomas in epidemiological data of odontogenic tumours around the world

Author/year	Hospital and country	*n*	Odontomas (%)	Ameloblastomas (%)
Regezi et al., 1978 [8]	Dental Hospital—USA	706	67	11
Gunhan et al., 1990 [1]	3 Medical Hospitals and 1 Dental Hospital—Turkey	409	20	40.3
Daley et al., 1994 [4]	Dental Hospital—Canada	392	51.5	13.5
Odukoya, 1995 [7]	Medical Hospital—Nigeria	289	4.2	58.5
Arotiba et al., 1997 [3]	Medical Hospital—Nigeria	128	–	59
Mosqueda-Taylor et al., 1997 [2]	1 Medical Hospital and 3 Dental Hospitals—Mexico	349	34.6	23.7
Yong Lu et al., 1998 [5]	Medical Hospital—China	759	6.7	58.6
Santos et al., 2001 [6]	Dental Hospital—Brazil	127	50.4	30.7

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firmation. Therefore, on these countries the incidence of odontomas probably is underestimated. On the other hand, ameloblastomas need a biopsy for confirmation of the diagnosis, and an official report. Surgery usually involves bone resection, performed by a dentist or a physician, in many countries in a Medical Hospital. Our present collaborative studies using data from Dental and Medical Hospitals, confirms this situation in Brazil. We are convinced this is also the explanation for some controversial results around the world.

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