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Dissertação

Avaliação de lesões intraósseas com diagnóstico clínico-imaginológico de periapicopatias crônicas: estudo retrospectivo multicêntrico

Carolina Clasen Vieira

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Orientadora: Ana Carolina Uchoa Vasconcelos

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Dissertação apresentada, como requisito parcial, para obtenção do grau de Mestre em Odontologia, Programa de Pós-Graduação em Odontologia, Faculdade de Odontologia de Pelotas, Universidade Federal de Pelotas.

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Notas Preliminares

A presente dissertação foi redigida segundo o Manual de Normas para Dissertações, Teses e Trabalhos Científicos da Universidade Federal de Pelotas de 2013, adotando o Nível de Descrição 4 – estrutura em Artigos, descrita no Apêndice D do referido manual. Acesso em: 20/01/2018.

Resumo

VIEIRA, Carolina Clasen. **Avaliação de lesões intraósseas com diagnóstico clínico-imaginológico de periapicopatias crônicas: estudo retrospectivo multicêntrico.** 2019. Dissertação (Mestrado em Odontologia) – Programa de Pós- Graduação em Odontologia da Universidade Federal de Pelotas.

As lesões periapicais representam sequelas de um processo de necrose pulpar, geralmente causado por cárie ou traumatismo dentário. Essas lesões endodônticas podem ser crônicas (cisto periapical, granuloma periapical ou abscesso crônico) ou agudas (periodontite apical ou abscesso periapical agudo) - e compreendem a radiolucência mais comumente encontrada nos maxilares. Entretanto, uma variedade de lesões intraósseas localizadas na região apical, não relacionadas à condição pulpar, pode ser clinicamente diagnosticada, de forma equivocada, como periapicopatias. A literatura afirma que aproximadamente 0,65% a 6,7% das lesões clinicamente diagnosticadas com origem endodôntica sejam lesões periapicais não endodônticas (LPNE). Considerando a importância de definir a prevalência e o perfil demográfico desses diagnósticos errôneos no Brasil, o objetivo do presente estudo multicêntrico foi determinar a frequência e as características clínicas de LPNE com diagnóstico clínico de periapicopatias, em três centros brasileiros de referência em patologia oral (Universidade Federal de Minas Gerais, Universidade Federal de Pelotas e Universidade Federal da Bahia), e discutir esses achados com aqueles descritos na literatura. Um estudo retrospectivo foi realizado por meio da coleta de dados oriundos de material enviado para análise anatomopatológica. Casos de diagnósticos histopatológicos de LPNE com diagnóstico clínico de patologias endodônticas foram recuperados. Dados referentes à idade, sexo e localização anatômica foram coletados. Além disso, foi realizada uma revisão da literatura sobre falhas diagnósticas endodônticas, publicadas em três bases de dados eletrônicas. Entre 66.179 biópsias orais, 7.246 (10.94%) foram diagnosticadas, clinicamente, como lesão periapical, dos quais 430 (5.93%) foram diagnosticados histopatologicamente como LPNE. A lesão mais frequente foi o cisto de origem odontogênica (n=124, 28.84%) seguido pelo ceratocisto odontogênico (n=107, 24.88%). A média de idade foi de 39.30 anos (variação de 6 a 80 anos). Duzentos e dezesseis (50.23%) casos acometeram o sexo masculino. A região póstero-mandibular foi observada em 174 (41.42%) casos informados. Uma variedade de diagnósticos histopatológicos, incluindo lesões císticas e tumorais odontogênicas e não odontogênicas, doenças infecciosas e neoplasias malignas foram observadas no presente estudo multicêntrico. As características apresentadas neste estudo foram consistentes com achados relatados na literatura.

Palavras-chave: Epidemiologia, Doença periapical, Granuloma Periapical, Cisto radicular.

Abstract

VIEIRA, Carolina Clasen. **Evaluation of intraosseous lesions with clinical and imaging diagnosis of cronic periapicopathies: a multicenter retrospective study.** 2019. Dissertation (Master degree in Dentistry) – Graduate Program in Dentistry, Federal University of Pelotas.

Most apical lesions are sequelae of pulpal necrosis usually caused by caries or dental trauma. These endodontic lesions may be chronic (periapical cyst, periapical granuloma or chronic abscess) or acute (periradicular abscess or cellulitis), and represent the most commonly encountered radiolucency in the jaws. However, a wide variety of intraosseous lesions located in the apical region, not related to the pulp condition can be clinically misdiagnosed as endodontic pathoses. Current literature suggests that approximately 0.65% to 6.7% of the lesions clinically diagnosed of endodontic origin are nonendodontic periapical lesions (NPL). Considering the importance of defining the relative incidence and demographic profile of these misdiagnoses in South America, the objective of the present multicenter study was to determine the frequency and clinical features of NPL with clinical diagnosis of endodontic lesions from three Brazilian representative geographical areas (Federal University of Minas Gerais, Federal University of Pelotas and Federal University of Bahia), and to discuss these findings in light of literature. A retrospective study was conducted. Cases of histopathological diagnoses of NPL with clinical diagnosis of endodontic pathoses were retrieved. Data regarding age, sex and anatomic site were collected. Additionally, a literature review regarding endodontic diagnostic failures published in three electronic databases was performed. Among 66,179 oral biopsies, 7,246 (10.94%) were clinically diagnosed as periapical disease, 430 (5.93%) of which cases were histopathologically diagnosed as NPL. The most frequent lesion was cyst of odontogenic origin (n=124, 28.84%) followed by odontogenic keratocyst (n=107, 24.88%). Mean age was 39.30 years (range: 6-80 years). Two hundred and sixteen (50.23%) cases occurred in males. Posterior lower jaws were observed in 174 (41.42%) informed cases. A wide variety of histopathological diagnoses, including benign odontogenic and non-odontogenic cystic and tumorous lesions, infectious diseases as well as malignant neoplasms was noted in the present multicentric survey. The features presented in this study were consistent with previous findings reported in the literature.

Keywords: Epidemiology, Periapical Diseases, Periapical Granuloma, Radicular Cyst.

SUMÁRIO

1 INTRODUÇÃO

A lesão perirradicular de origem endodôntica representa um processo inflamatório dos tecidos periapicais associada à infecção e necrose do sistema de canais radiculares. A formação de lesões inflamatórias periapicais constitui uma reação secundária à infecção no canal radicular, com a disseminação dos produtos tóxicos relacionados em direção à zona apical (NEVILLE, DAMM, ALLEN & CHI, 2016).

Estima-se que, aproximadamente, 73% das lesões radiolúcidas maxilares sejam classificadas como cistos radiculares, granulomas ou abcessos perirradiculares (KOIVISTO et al., 2012). Em geral, pacientes portadores de lesões periapicais crônicas não apresentam sinais e sintomas de ordem sistêmica, a menos que ocorra uma exacerbação inflamatória aguda. O elemento dentário associado responde negativamente ao teste de vitalidade pulpar ou revela um resultado positivo retardado e, usualmente, apresenta dor à percussão. Radiograficamente, cistos e granulomas periapicais evidenciam aspecto similar, representado por área radiolúcida, bem delimitada, de tamanho variado, com ou sem a presença de halo radiopaco circundante. Ainda, pode-se observar deslocamento dentário e reabsorção radicular. O diagnóstico definitivo é dado por meio da análise histopatológica (BECCONSALL-RYAN, K., TONG, D. & LOVE, R., 2010; M.NEVILLE, DAMM, ALLEN & CHI, 2016).

A literatura aponta que 0,65% a 6,7% das lesões localizadas em região periapical, porém de origem não endodôntica, são diagnosticadas clinica e imaginologicamente como periapicopatias (BHASKAR, 1966; KONTOGIANNIS, 2014; ORTEGA, 2007; NOBUHARA, 1993). Dentre essas, observam-se cistos e tumores de origem não endodôntica como ceratocisto odotogênico, cisto do ducto nasopalatino e ameloblastoma, neoplasias benignas e malignas de origem glandular, carcinoma espinocelular além de lesões metastáticas (FAITARONI et al, 2011; HILFER et al., 2013; REKABI et al., 2013 SILVA et al., 2017).

Diante das patologias de origem não endodôntica que podem mimetizar periapicopatias, é fundamental realizar anamnese detalhada, além

de exame clínico e imaginológico a fim de minimizar possíveis falhas diagnósticas, sobretratamento ou tratamento ineficaz. Assim, o objetivo do presente trabalho é determinar a frequência e analisar as características clínicas das lesões periapicais não endodônticas com diagnóstico clínico-imaginológico de periapicotpatias, em três centros brasileiros de referência em patologia oral.

2 OBJETIVOS

2.1 Objetivo Geral

Realizar um estudo retrospectivo dos casos diagnosticados clinicamente (clínico-imaginológico) como cisto radicular, granuloma e abcesso perirradicular em três centros de referência em patologia oral.

2.2 Objetivos Específicos

2.2.1 Determinar a frequência das lesões periapicais diagnosticadas, clinica e imaginologicamente, como de origem endodôntica com diagnóstico histopatológico distinto de periapicopatias.

2.2.2 Descrever as características demográficas da população diagnosticada, clinica e imaginologicamente, como lesão periapical de origem endodôntica com diagnóstico histopatológico distinto de periapicopatias.

2.2.3 Realizar uma revisão da literatura acerca dos casos diagnosticados clinica e imaginologicamente de forma equivocada como lesões periapicais de origem endodôntica.

2.2.4 Comparar os dados obtidos no presente estudo multicêntrico com aqueles obtidos na revisão da literatura.

3 PROJETO DE PESQUISA

3.1 Materiais e métodos

3.1.1 Delineamento e Aspectos éticos

O estudo se insere no método de estudo transversal retrospectivo. O presente projeto será submetido à aprovação do Comitê de Ética em Pesquisa (CEP) da Faculdade de Odontologia da Universidade Federal de Pelotas (FO-UFPel).

3.1.2 Seleção de casos

Os casos selecionados serão obtidos por meio de levantamento epidemiológico dos registros contidos nas fichas de biópsia do Centro de Diagnóstico das Doenças da Boca (CDDB) da Faculdade de Odontologia da Universidade Federal de Pelotas, no período compreendido entre o ano de 1953 até outubro de 2018. Os casos incluídos serão aqueles com diagnóstico inicial de cisto radicular/periapical, granuloma periapical e abcesso periapical/perirradicular. Para todas as fichas que atenderem aos critérios de inclusão, serão coletados (quando disponível) os dados referentes a sexo, idade, localização da lesão e aspectos radiográficos. Para determinar a localização da lesão, os maxilares serão classificados em: I) região anterior – de canino a canino e II) região posterior – pré-molares, molares e ramo (quando em mandíbula). Para confirmação do diagnóstico, quando necessário, as lâminas histopatológicas referentes aos casos levantados serão revisadas por um patologista experiente.

3.1.3 Revisão da Literatura

A revisão da literatura será realizada considerando estudos publicados em língua inglesa, espanhola e portuguesa que incluam casos com diagnóstico clínico de periapicopatias cuja análise anatomopatológica revelasse lesão não endodôntica. Não haverá restrição por idade, sexo ou ano de publicação. Estudos não disponíveis para leitura completa serão excluídos. A revista da literatura será realizada por meio de três bases de dados: PubMed/Medline, Web of Science e Scopus. A busca na base de dados PubMed será conduzida por termos MeSH com as seguintes palavras-

chaves e entretermos: (Periapical Abcess)[MeSH] OR (Dentoalveolar Abscess, Apical) OR (Abscess, Apical Dentoalveolar) OR (Abscesses, Apical Dentoalveolar) OR (Apical Dentoalveolar Abscess) OR (Apical Dentoalveolar Abscesses) OR (Dentoalveolar Abscesses, Apical) OR (Periodontitis, Apical, Suppurative) OR (Periapical Periodontitis, Suppurative) OR (Periapical Periodontitides, Suppurative) OR (Periodontitides, Suppurative Periapical) OR (Periodontitis, Suppurative Periapical) OR (Suppurative Periapical Periodontitides) OR (Suppurative Periapical Periodontitis) OR (Alveolar Abscess, Apical) OR (Abscess, Apical Alveolar) OR (Abscesses, Apical Alveolar) OR (Alveolar Abscesses, Apical) OR (Apical Alveolar Abscess) OR (Apical Alveolar Abscesses) OR (Abscess, Periapical) OR (Abscesses, Periapical) OR (Periapical Abscesses) OR (Periapical Lesion) OR (Periapical Lesions) AND (Periapical Granuloma)[Mesh] OR (Granuloma, Periapical) OR (Granulomas, Periapical) OR (Periapical Granulomas) OR (Periapical Periodontitis, Chronic Nonsuppurative) OR (Periodontitis, Apical, Chronic Nonsuppurative) OR (Dental Granulomas) OR (Granulomas, Dental) OR (Dental Granuloma) OR (Granuloma, Dental) AND (Radicular Cyst)[Mesh] OR (Cyst, Radicular) OR (Cysts, Radicular) OR (Radicular Cysts) OR (Periapical Cyst) OR (Cyst, Periapical) OR (Cysts, Periapical) OR (Periapical Cysts) OR (Periodontal Cyst, Apical) OR (Apical Periodontal Cyst) OR (Apical Periodontal Cysts) OR (Cyst, Apical Periodontal) OR (Cysts, Apical Periodontal) OR (Periodontal Cysts, Apical) AND (Epidemiology)[MeSH] OR (epidemiology") [Subheading] OR (epidemics) OR (frequency) OR (surveillance) OR (morbidity) OR (occurrence) OR (outbreaks) OR (prevalence) OR (endemics) OR (incidence) AND (Prevalence)[Mesh] OR (Prevalences).

Os estudos identificados serão inseridos no *software* EndNote (Thompson Reuters, Nova York, NY, USA). Após remoção das duplicatas, a seleção dos estudos será desenvolvida como citado anteriormente.

3.1.4 Análise estatística

Os dados obtidos serão tabulados em planilha eletrônica no *software* Excel (Microsoft, versão 15.0, Albuquerque, Novo México, EUA) e avaliados

através do programa *Statistical Package for the Social Sciences* (SPSS) (Statistical Package for the Social Sciences, Chicago, IL, EUA), versão 22.0. Será realizada uma análise descritiva dos dados e testes estatísticos serão aplicados de acordo com a normalidade da amostra.

3.2 Orçamento

Produto	**Quantidade**	**Valor em reais (R$) (outubro/2017)**
Canetas	3 unidades	4,00
Computador Dell	1 unidade	**
Folhas de ofício	1 resma	15,00
Impressão da dissertação	6 cópias	170,00
Microscópio de captura	1 unidade	*
Software SPSS 22.0	1 unidade	**
Software EndNote	1 unidade	**
	Total	189,00

* Cedido pela UFPel

** Cedido pelos pesquisadores responsáveis

3.3 Cronograma

Ano/mês	**2018**					**2019**				
Atividade	Ago	Set	Out	Nov	Dez	Jan	Fev	Mar	Abr	Mai
Revisão da Literatura										
Elaboração do Projeto										
Submissão ao CEP										
Levantamento dos casos										
Análise dos resultados										
Elaboração do artigo científico										
Submissão do artigo científico										

3.4 Referências

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4 RELATÓRIO DE CAMPO

4.1 Estudo multicêntrico

O estudo foi submetido ao Comitê de Ética e Pesquisa da Faculdade de Medicina da Universidade Federal de Pelotas em 2018 como um estudo de único centro realizado pela UFPEL. Porém, após a aprovação, se obteve o ingresso de outras duas universidades na elaboração do estudo: a Universidade Federal de Minas Gerais (UFMG) e a Universidade Federal da Bahia (UFBA), tornando o estudo multicêntrico.

4.2 Análise estatística

Devido a heterogeneidade dos dados coletados, não se realizou nenhum teste estatístico. Foi feita apenas uma análise descritiva dos resultados.

4 ARTIGO

O seguinte artigo foi formatado de acordo com as normas da revista *Clinical Oral Investigations* – Qualis A1 e fator de impacto 2.386, e submetido para publicação.

The title of the article: A retrospective multicentre study of periapical lesions misdiagnosed as endodontic origin

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A retrospective multicenter study of periapical lesions misdiagnosed as of endodontic origin

Abstract

Objectives: To analyze the features of lesions clinically misdiagnosed as endodontic periapical pathoses and to discuss these findings in light of the literature.

Materials and Methods: A retrospective study was conducted on biopsies obtained from 1953 to 2018 at three Brazilian oral and maxillofacial pathology centers. Cases of histopathological diagnoses of nonendodontic periapical lesions (NPL) with clinical diagnosis of endodontic pathoses were retrieved. Data regarding age, sex and anatomic site were collected. Additionally, a literature review regarding endodontic diagnostic failures published in three electronic databases was performed.

Results: Among 66,179 oral biopsies, 7,246 (10.94%) were clinically diagnosed as periapical disease, 430 (5.93%) of which cases were histopathologically diagnosed as NPL. The most frequent lesion was cyst of odontogenic origin (n=124, 28.84%) followed by odontogenic keratocyst (n=107, 24.88%). Mean age was 39.30 years (range: 6-80 years). Two hundred and sixteen (50.23%) cases occurred in males. Posterior lower jaws were observed in 174 (41.42%) informed cases.

Conclusions: A wide variety of histopathological diagnoses, including benign odontogenic and non-odontogenic cystic and tumorous lesions, infectious diseases as well as malignant neoplasms was noted in the present survey.

The features presented in this study were consistent with previous findings reported in the literature.

Clinical relevance

This study serves to inform clinicians regarding the diversity of lesions that can mimic periapical pathoses, including malignant diseases, and to highlight the importance of histopathological evaluation of lesional tissue.

Keywords: Misdiagnosis, Epidemiology, Periapical Diseases, Periapical Granuloma, Radicular Cyst.

Introduction

Most apical lesions are sequelae of pulpal necrosis usually caused by caries or dental trauma [1]. These endodontic lesions may be chronic (periapical cyst, periapical granuloma or chronic abscess) or acute (periradicular abscess or cellulitis), and represent the most commonly encountered radiolucency in the jaws [2]. However, a wide variety of intraosseous lesions located in the apical region, not related to the pulp condition can be clinically misdiagnosed as endodontic pathoses [3].

Current literature suggests that approximately 0.65% to 6.7% of the lesions clinically diagnosed of endodontic origin are nonendodontic periapical lesions (NPL) [2-7]. In order to minimize diagnostic failures, it is essential to perform careful detailed anamnesis, considering patient's medical and dental history as well as detailed physical and image examination. In addition, it is important to know the pathologies that are not related to pulp necrosis but can mimic endodontic lesions.

Considering the importance of defining the relative incidence and demographic profile of these misdiagnoses in South America, the objective of the present multicenter study was to determine the frequency of NPL with clinical diagnosis of endodontic lesions from three Brazilian representative geographical areas. To the best of our knowledge, this is the first and the largest multicenter study in this scope. This study also discusses the global condition of the demographic distribution and clinical characteristics of this kind of diagnostic failure in light of current literature.

Materials and methods

Multicenter study

Ethical issues and study design

The present study was approved by the Ethics Committee of the Federal University of Pelotas (No. 2.887.524) and was conducted in accordance with the guidelines of the Declaration of Helsinki. A total of 66,179 biopsy records were obtained from a consortium of three oral and maxillofacial pathology services from three regions of Brazil: Department of Oral Pathology of the Federal University of Bahia (Northeast region), Department of Oral Pathology and Surgery of the Federal University of Minas Gerais (Southeast region) and Diagnostic Center for Oral Diseases of the Federal University of Pelotas (South region). It was a retrospective analysis of case records from 1953 to 2018. The sources of the cases reviewed at the three Brazilian oral and maxillofacial pathology centers are detailed in Table 1.

Sample

Cases with clinical diagnoses of periapical cyst, periapical granuloma or dentoalveolar abscess, which were histopathologically diagnosed with nonendodontic pathologic entity were recovered. The research of the data was carried out by 6 researchers, being two of each center. All histopathological diagnoses were performed by six independent oral and maxillofacial pathologists with more than 20 years of experience. Data regarding patient age, sex and anatomical location were obtained from patients' records. To establish the location of the lesions, the jaws were classified into: 1) anterior: lesions in the incisor/canine region and 2) posterior: lesions in premolar/molar retromolar/ramus/maxillary sinus region. Lesions

were classified according to the 2017 classification of the World Health Organization (WHO) [8].

Literature review

Information sources, eligibility criteria and search

A review of the literature with no restriction of publication year was performed to retrieve studies regarding NPL clinically misdiagnosed as endodontic periapical pathoses. Exclusion criteria were 1) studies in languages other than English, Spanish or Portuguese and 2) studies with no available full text. Studies that did not provide data about sex, age and histopathological diagnosis were also excluded. PubMed (National Library of Medicine), Web of Science (Thomson Reuters) and Scopus (Elsevier) electronic databases were searched to identify studies that could be included. The queries were performed in September 2018 using Mesh and the following entry terms and keywords: ((((((((((Periapical Granuloma)[Mesh] OR (Granuloma, Periapical) OR (Granulomas, Periapical) OR (Periapical Granulomas) OR (Periapical Periodontitis, Chronic Nonsuppurative) OR (Periodontitis, Apical, Chronic Nonsuppurative) OR (Dental Granulomas) OR (Granulomas, Dental) OR (Dental Granuloma) OR (Granuloma, Dental) AND ((((((((((((Radicular Cyst)[Mesh] OR (Cyst, Radicular) OR (Cysts, Radicular) OR (Radicular Cysts) OR (Periapical Cyst) OR (Cyst, Periapical) OR (Cysts, Periapical) OR (Periapical Cysts) OR (Periodontal Cyst, Apical) OR (Apical Periodontal Cyst) OR (Apical Periodontal Cysts) OR (Cyst, Apical Periodontal) OR (Cysts, Apical Periodontal) OR (Periodontal Cysts, Apical) AND ((((((((((Epidemiology) [MeSH] OR (epidemiology") [Subheading] OR (epidemics) OR (frequency) OR (surveillance) OR (morbidity) OR

(occurrence) OR (outbreaks) OR (prevalence) OR (endemics) OR (incidence) AND ((Pathology)[MeSH] OR (Pathologies) AND ((((((Diagnostic Errors)[MeSH] OR (Diagnostic Error) OR (Error, Diagnostic) OR (Errors, Diagnostic) OR (Misdiagnosis) OR (Misdiagnoses). The identified studies were managed in the EndNote software (Thompson Reuters, New York, NY, USA). After removal of duplicates, selection of studies was performed in two phases: 1) Titles/abstracts that met the eligibility criteria were included. If a title/abstract provided insufficient information for a decision about inclusion/exclusion, the study was included; 2) the included studies were selected according to inclusion/exclusion criteria after full text reading. In addition, manual searches were conducted by cross-checking the reference lists of the included articles in order to identify publications that may have been missed during the electronic searches.

Data extraction and items

The following data were extracted from the articles included in the literature review: author and year of publication, country, number of cases reported, patient's sex and age, anatomical location and histopathological diagnoses.

Data analysis

Data analysis was performed using the Stata 12.0 software (StataCorp, College Station, TX, USA). Descriptive statistics were used to characterize the cases with respect to the following information: patient's sex and age and lesion's anatomical location.

Results

Multicenter study

Within a 65-year period, a total of 66,179 oral biopsies were performed at the centers studied, 7,246 (10.94%) of which were clinically diagnosed as periapical lesions of endodontic origin. A total of 6,710/7,246 (92.60%) were histologically diagnosed with radicular cyst, granuloma or dentoalveolar abscess, while 430 (5.93%) were histopathologically diagnosed as NPL. One hundred and six lesions (1.46%) were excluded due to inconclusive diagnosis and insufficient/inadequate material for histopathological analysis.

The frequency and demographic data of NPL patients are shown in Table 2. Thirty-two different histopathological diagnoses were observed. The most common lesion was cyst from odontogenic origin (CO) (124, 28.84%), followed by odontogenic keratocyst (OK) (107, 24.88%) and dentigerous cyst (48, 11.16%). Squamous cell carcinoma was the most frequent malignant lesion. A total of 216 (50.23%) cases occurred in males and 214 (49.77%) in females (male-to-female ratio: 1:1). The mean age at diagnosis was 39.30 years with a range between 6 and 80 years. Regarding location, of the 420 informed cases, 174 (41.42%) were in the posterior mandible, 108 (25.71%) in the anterior maxilla, 95 (22.61%) in the posterior maxilla and 43 (10.23%) in the anterior mandible.

Literature review

The literature review yielded 6,692 articles, and 58 articles were selected after applying the inclusion and exclusion criteria. The authors separated the results between series or case reports and retrospective

laboratorial researches (biopsy records), in order to provide a better understanding and comparison of the data.

Five articles comprised retrospective analysis of biopsy records (Table 3). Three were performed in America [1, 4, 6], one in Europe [7] and one in Asia [3]. The prevalence of NPL varied from 0.65% to 3.42%. Two studies included the mean age of patients; patients in these studies were in the 30s [1] and 40s [7]. Two studies revealed predilection for males. The most frequent location of NPL was the mandible in two studies [3, 4]. OK was the most frequent lesion observed in three of the five studies [3, 6, 7]. Squamous cell carcinoma, metastatic carcinoma, plasmacytoma and Langerhans cell histiocytosis were the most prevalent (or unique) malignant lesions showed in these studies.

The case reports were published in four continents: Americas (37 cases), Asia (25 cases), Europe (14 cases) and Oceania (2 cases), totaling 78 cases. Of those, twenty-seven, were from Brazil - corresponding to 34.61% of this sample. The mean age was 24.05 (12-64) years. Forty-five (57.69%) studies reported cases in males and 33 (42.30%) in females. Regarding the anatomical site, 32 (41.02%) cases occurred in the posterior mandible, 26 (33.33%) in the anterior maxilla, 15 (19.23%) in the anterior mandible and five (6.41%) in the posterior maxilla (Figure 1).

Discussion

Current literature shows that lesions resulting from dental pulp necrosis are the most common pathoses located in the alveolar bone [3, 9, 10]. Several studies have indicated that between 85% and 95% of complications

resulting from pulpal necrosis respond to conservative root canal treatment [11, 12]. However, some studies have reported pathologic entities associated with root apexes without relationship to the pulp condition [13-18]. In the present multicenter study, 430 cases of NPL clinically misdiagnosed as endodontic lesions have been added to the literature.

In this Brazilian collaborative survey, NPL represented 0.64% of cases of the entire sample, and 5.93% of the cases among the 7,216 lesions that were clinically diagnosed with periapical pathoses. these rates are higher than those reported in other similar single center studies in America, Europe and Asia, which show a relative frequency of misdiagnosis ranging from 0.65 to 3.42% [1, 3, 6, 7]. Direct comparison of the real prevalence of this diagnostic failure among studies based on biopsy records in different regions may be limited, because inclusion and exclusion criteria vary and differences on the number of the samples and divergences on criteria used for histopathological diagnosis are evident [19]. Of note, the strength of the present study lies on the inclusion of the largest sample of these endodontic diagnostic failures.

The present multicenter research demonstrated a wide age range of affected people. The youngest patient was 6 years old, and the oldest was 80. Most individuals were in the fifth decade of their life, in agreement with a study published in Greece [7]. Other studies also reported a large age range [3, 6] that could be explained by the different nature of the lesions. Although some previous reports have shown a female preference for misdiagnoses involving periapical pathoses [4, 6], two of the five selected retrospective studies based on biopsy records have demonstrated a male prevalence [1, 3]. In our multicenter study, there was a slight male prevalence (male-to-female ratio:

1.2:1). It is difficult to identify the reasons that could explain this slight disparity between sexes. To our knowledge, this multicenter study involves a significant number of cases, and the discrepancy between sexes, indeed, might not exist, a fact also supported by a Canadian study with a smaller sample [1].

Regarding the anatomical location, in our study, NPL was more commonly found in the posterior mandible followed by the anterior maxilla. The mandible was more affected in two of the four retrospective studies, based on biopsy records that included the location of the lesion; however, these studies did not provide information regarding the region of the jaws [1]. The majority of mandible lesions can be explained by the most prevalent NPL: three of the five retrospective studies based on biopsy records showed that odontogenic OK was the most common lesion. Several epidemiological studies suggest that OK is located in the posterior mandible in approximately 70–80% of cases [20-22].

The present multicenter study identified thirty-two different NPLs, including neoplasms of salivary glands, odontogenic cysts and tumors, benign bone pathologies, developmental cysts, infectious diseases as well as malignant neoplasms. CO was the most prevalent NPL in the present multicenter study. CO comprises a large number of lesions which, despite the presence of odontogenic epithelium, could not be specifically diagnosed mainly because of the absence of clinical and radiographic information. The second most frequent NPL observed in the present multicenter survey was OK, corroborating findings observed in similar studies conducted in Taiwan, Greece and Chile [3, 6, 7]. However, these single-center studies did not report

whether histopathological diagnostic doubts, such as those observed when OC is histopathologically diagnosed, were included in their samples. Epidemiological reports, after the last WHO classification of Odontogenic and Maxillofacial Bone Tumors, described OK as the second most frequent developmental odontogenic cyst after dentigerous cyst. Because of the potential for growth, frequent recurrence and association with nevoid basal cell carcinoma syndrome or Gorlin syndrome [23, 24], periapical radiolucencies that do not heal after root canal treatment or with an incomplete clinical history or with unusual radiographic image should undergo surgical treatment and biopsy.

There were no malignant cases of NPL in three of five previous laboratorial studies [1, 4, 6]; however, it is worth noting that the present study comprised of the lower number of cases of malignancy being similar to that reported by Kontogiannis et al [6]. Similar to the present collaborative study, Huang et al found that squamous cell carcinoma was the most prevalent malignant NPL, followed by malignant neoplasms of salivary glands. Langerhans cell histiocytosis and plasmacytoma were detected at the Brazilian centers studied and in the literature review. However, since there is no consensus about the classification of these diseases as malignant, the cases were not included as malignant lesions in the literature review.

According to our literature review, 78 case reports were retrieved comprising of twenty-five different NPLs. Male individuals, third decade of life and the posterior mandible were the sex, mean age and the location most commonly found. With the exception of mean age, the present multicenter study is in agreement with the published clinical cases. However, this

comparison should be performed with caution due to the different nature of the data. In addition, the most frequent lesion was OK, and the majority of misdiagnosed cases was reported in America. All cases published in South America were from Brazil. No case was observed in the continent of Africa. The authors raised the hypothesis that South America's research strength may be underestimated, because their studies are often published in journals that are not indexed in major databases.

In summary, this multicenter study showed that a wide variety of pathoses were clinically misdiagnosed as endodontic lesions. The present research has added more than four hundred cases of NPL to the literature, providing novel data on the clinicopathological features of this diagnostic failure. In our study, similarities regarding sex, age and location of the affected individuals were found in comparison with retrospective studies based on biopsy records and case series reported elsewhere. The authors stress that tissues removed from routine enucleation or curettage of periapical lesions must be submitted to histopathological examination.

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Table 1. Sources of cases reviewed at three Brazilian oral and maxillofacial pathology centers

Institution	*State*	*Geographic Areas (Km^2)*[a]	*Population (millions)*	*Period*	*Number of biopsy lesions*	*Lesions with clinical/imaging diagnosis of endodontic pathoses (n)%*[b]	*Lesions with histopathological diagnosis of endodontic pathoses (n)%*[c]	*Lesions with histopathological diagnosis of NPL (n)%*[d]
UFPel[e]	Rio Grande do Sul	281.737	11.329.605	1959-2018	25.090	5137 (20.47%)	4.853 (19.34%)	193 (0.76%)
UFMG[f]	Minas Gerais	586.520	21.040.662	1953-2018	37.636	1809 (4.80%)	1.578 (4.19%)	218 (0.57%)
UFBA[g]	Bahia	564.732	14.812.617	2001-2018	3.453	300 (8.68%)	279 (8.07%)	19 (0.55%)
TOTAL	-	-	**-**	**-**	**66.179**	**7.246 (10.94%)**	**6.710 (10.13%)**	**430 (0.64%)**

[a] Data according to the Brazilian Institute of Geography and Statistics (IBGE), 2017; [b,c,d] Percentage of the whole sample; [e] Diagnostic Centre for Oral Diseases of the Federal University of Pelotas (South region);[f] Department of Oral Surgery and Pathology, School of Dentistry of the Federal University of Minas Gerais (South-East region); [g]Department of Oral and Maxillofacial Pathology, School of Dentistry of the University of Bahia (North-East region).

Table 2: Clinical features of NPLs diagnosed at three Brazilian oral and maxillofacial pathology centers

Histopathological diagnosis	***Number***	***(%)[a]***	***Age range (Years)***	***Sex***		***Location***			
				Male	*Female*	*Maxilla [a]*	*Maxilla [p]*	*Mandible [a]*	*Mandible [p]*
Cyst of odontogenic origin	124	28.84	41.09	69	55	41	36	6	37
Odontogenic Keratocyst	107	24.88	46.26	57	50	16	22	15	53
Dentigerous Cyst	48	11.16	26.10	24	24	4	12	0	31
Nasopalatine Duct Cyst	28	6.55	47.03	20	8	25	3	0	0
Ameloblastoma	27	6.28	33.84	10	17	0	2	5	20
Central Giant Cell Granuloma	22	5.12	36.72	7	15	8	2	4	7
Benign Fibro-osseous Lesion	13	3.02	40.81	2	11	1	1	2	8
Actinomycosis	7	1.63	38.14	3	4	3	2	1	0
Calcifying Odontogenic Cyst	7	1.63	48.85	5	2	1	3	0	2
Lateral Periodontal Cyst	7	1.63	54.66	4	3	1	0	3	3
Traumatic Bone Cyst	5	1.16	50.25	0	5	0	1	0	4
Adenomatoid Odontogenic Tumor	4	0.93	24.75	2	2	0	2	1	1

Squamous Cell Carcinoma	3	0.70	52.33	3	0	2	1	0	0
Focal Osteoporotic Defect	3	0.70	42.0	1	2	0	0	0	3
Glandular Odontogenic Cyst	2	0.47	56.5	0	2	1	0	1	0
Mucoepidermoid Carcinoma	2	0.47	27.0	0	2	0	2	0	0
Ossifying Fibroma	2	0.47	33.5	0	2	0	0	2	0
Cystic Glandular Hyperplasia	2	0.47	28.0	1	1	1	0	0	1
Metastasis of Adenoid Cystic Carcinoma	2	0.47	49.0	1	1	0	0	1	1
Adenoid Cystic Carcinoma	2	0.47	27.0	1	1	1	1	0	0
Maxillary Sinus Mucocele	2	0.47	51.0	1	1	0	2	0	0
Canalicular Adenoma	1	0.23	68.0	0	1	0	1	0	0
Pleomorphic Adenoma	1	0.23	31.0	0	1	0	1	0	0
Acinar Cell Carcinoma	1	0.23	65.0	0	1	1	0	0	0
Central Odontogenic Fibroma	1	0.23	12.0	1	0	0	0	1	0
Clear Cell Carcinoma	1	0.23	76.0	0	1	0	0	0	1

Histiocistosis	1	0.23	21.0	0	1	0	0	0	1
Fibrosis Dysplasia	1	0.23	27.0	1	0	0	0	1	0
Odontoma	1	0.23	16.0	1	0	1	0	0	0
Sinusitis	1	0.23	19.0	0	1	0	1	0	0
Odontogenic Myxoma	1	0.23	29.0	1	0	0	0	0	1
Squamous Odontogenic Tumor	1	0.23	39.0	1	0	1	0	0	0
TOTAL	430	-	**39.30**	**216 (50.23%)**	**214 (49.77%)**	**108* (25.71%)**	**95* (22.61%)**	**43* (10.23%)**	**174* (41.42%)**

*N=420 informed cases
[a] anterior, [b] posterior

Table 3. Demographic data of retrospective studies from biopsy records published in the literature

Authors (year of publication)	***Country***	***Total number of cases (n)***	***NPL n (%)****	***Mean age***	***Most prevalent sex (%)***	***Most frequent location (%)***	***Most frequent NPL (%)****	***Most frequent malignant NPL (%)****
Bhaskar et al. (1966)	USA	2308	53 (2.30)	NI	Female (62.75%)	Mandible (52.00%)	Cementoma (1.21%)	Not found
Kuc et al (2000)	Canada	805	8 (1.00)	37.40	Male=Female (50%)	NI	Central giant cell granuloma (0.24%)	Not found
Ortega et al (2007)	Chile	4006	26 (0.65)	NI (9-76)	Female (57.69%)	Maxilla (61.54%)	Odontogenic keratocyst (0.27%)	Not found
Kontogiannis et al. (2015)	Greece	1521	52 (3.42)	47.29	Male (57.69%)	Maxilla (56.00%)	Odontogenic keratocyst (1.18%)	Metastatic carcinoma (0.06%)
Huang et al. (2016)	Taiwan	4004	115 (2.95)	NI (8-83)	Male (53.39%)	Mandible (61.02%)	Odontogenic keratocyst (0.94%)	Squamous Cell Carcinoma (0.17%)
Present study	**Brazil**	**7246**	**430 (5.93)**	**39.30**	**Male (50.23%)**	**Mandible (51.65%)**	**Odontogenic cyst (1.71%)**	**Squamous Cell Carcinoma (0.04%)**
TOTAL	-	19890	**684 (3.43)**	**-**	**-**	**-**	**-**	**-**

NI: not informed; n: number of the whole sample;* percent of total number of cases

Figure 1. Demographic data of case reports published in the literature

5 CONSIDERAÇÕES FINAIS

A partir do presente estudo pode-se concluir que uma variedade de lesões intraósseas, benignas e malignas, localizadas na região periapical dos maxilares e não relacionadas à condição pulpar, podem mimetizar, clinicamente, periapicopatias crônicas. Desta forma, os clínicos devem estar atentos para a realização de uma anamnese e exame clínico detalhados, somado ao acompanhamento de lesões radiolúcidas periapicais de dentes submetidos a tratamento endodôntico, com a finalidade de minimizar falhas diagnósticas. Adicionalmente, os resultados deste estudo reforçam a importância da avaliação anatomatológica de espécimens com diagnóstico clínico de periapicopatias.

Anexos

Anexo A – Aprovação do Comitê de Ética e Pesquisa da Faculdade de Medicina da Universidade Federal de Pelotas

UFPEL - FACULDADE DE MEDICINA DA UNIVERSIDADE FEDERAL DE PELOTAS

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Avaliação de lesões intraósseas com diagnóstico clínico-imaginológico de periapicopatias: estudo retrospectivo

Pesquisador: Ana Carolina Uchoa Vasconcelos

Área Temática:

Versão: 1

CAAE: 96857918.1.0000.5317

Instituição Proponente: Faculdade de Odontologia

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.887.524

Apresentação do Projeto:

A lesão perirradicular de origem endodôntica constitui-se como uma inflamação e destruição dos tecidos periapicais associada à infecção e necrose do sistema de canais radiculares. Aproximadamente 73% das lesões radiolúcidas maxilares são classificadas como cistos radiculares, granulomas e abcessos perirradiculares. Apesar das semelhanças clínico-imaginológicas, o diagnóstico de cistos e granulomas periapicais é dado por meio da
análise histopatológica. A literatura aponta que cerca de 0,65% até 6,7% das lesões periapicais de origem não endodôntica são diagnosticadas, clinicamente, como periapicopatias. Diante das inúmeras patologias de origem não endodôntica que podem ser confundidas com periapicopatias, é fundamental realizar uma anamnese detalhada, além de exames clínico e imaginológicos. Na tentativa de evitar um sobretratamento ou tratamento
ineficaz, é importante reconhecer as patologias que podem mimetizar uma lesão perirradicular de origem endodôntica.

Objetivo da Pesquisa:

Objetivo Primário:

Realizar um estudo retrospectivo dos casos diagnosticados clinicamente (diagnóstico clínico-radiográfico) como cisto radicular, granuloma e abcesso perirradicular em um serviço de referência em patologia oral, durante um período de 58 anos.

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Anexo B – Normas para submissão no periódico *Clinical Oral Investigations*

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Department of Parodontology and Conservative Dentistry
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Cartwright J (2007) Big stars have weather too. IOP Publishing PhysicsWeb. http://physicsweb.org/articles/news/11/6/16/1. Accessed 26 June 2007

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Anexo C – Comprovante de submissão do artigo à revista *Clinical Oral Investigation*

Clinical Oral Investigations - Submission Notification to co-author

Clinical Oral Investigations <em@editorialmanager.com>
Ter, 22/01/2019 11:16
Você

Re: "A retrospective multicentre study of periapical lesions misdiagnosed as endodontic origin"
Full author list: Carolina Vieira; Fernanda Pappen; Laura Kirschnick; Mariana Cademartori; Aline do Couto; Lauren Schuch; Leonardo Melo; Jean dos Santos; maria de Aguiar; ana Vasconcelos

Dear Ms Carolina Vieira,

We have received the submission entitled: "A retrospective multicentre study of periapical lesions misdiagnosed as endodontic origin" for possible publication in Clinical Oral Investigations, and you are listed as one of the co-authors.

The manuscript has been submitted to the journal by Dr. Dr. ana Vasconcelos who will be able to track the status of the paper through his/her login.

If you have any objections, please contact the editorial office as soon as possible. If we do not hear back from you, we will assume you agree with your co-authorship.

Thank you very much.

With kind regards,

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