UNIVERSIDADE ESTADUAL DE CAMPINAS
FACULDADE DE ODONTOLOGIA DE PIRACICABA

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ANÁLISE DAS CARACTERÍSTICAS CLINICOPATOLÓGICAS DE DISPLASIAS FIBROSAS E FIBROMAS OSSIFICANTES CENTRAIS ENVOLVENDO MANDÍBULA E MAXILA. ESTUDO COLABORATIVO INTERNACIONAL.

Tese apresentada à Faculdade de Odontologia de Piracicaba, da Universidade Estadual de Campinas, para obtenção do Título de Doutor em Estomatopatologia, Área de concentração em Patologia.

Orientador: Pablo Agustin Vargas

Este exemplar corresponde à versão final da Tese defendida pela aluna, e orientada pelo Prof. Dr. Pablo Agustin Vargas.

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"Quem eu sou, você só vai perceber quando olhar nos meus olhos, ou melhor, além deles."

Clarice Lispector

RESUMO

A displasia fibrosa (DF) e o fibroma ossificante central (FOC) fazem parte de um grupo de lesões conhecido como fibro-ósseas benignas (LFOB) e afetam principalmente a maxila, a mandíbula e ossos da região craniofacial. Caracterizam-se pela substituição do tecido ósseo normal por uma matriz de tecido conjuntivo fibroso com níveis variados de material mineralizado. As DFs e os FOCs costumam apresentar características clínicas e histopatológicas similares, entretanto, possuem padrões distintos de progressão e comportamento biológico. Portanto é muito importante fazer a distinção diagnóstica entre estas lesões. Este trabalho teve como objetivos analisar e comparar as características demográficas, clínicas, imaginológicas e histopatológicas de pacientes diagnosticados com DFs e FOCs. Foi realizada uma análise retrospectiva internacional e multi-institucional que selecionou 68 casos de DF e 37 casos de FOC e permitiu o estudo de características clinicopatológicas. As DFs (n=41; 60,2%) e os FOCs (n=24; 64,9%) foram mais comuns em pacientes do gênero feminino na segunda e terceira década de vida. As DFs acometeram preferencialmente a maxila (n=38; 56%) e os FOCs a mandíbula (n=23; 62,2%). Com relação aos aspectos imaginológicos, as DFs apresentaram-se predominantemente como lesões radiopacas com limites mal definidos e os FOCs como lesões radiolúcidas bem delimitadas. Microscopicamente, foi possível evidenciar continuidade do osso lesional com a cortical óssea de revestimento nas DFs e, interessantemente, um fenômeno de separação entre as trabéculas ósseas lesionais e o estroma adjacente também foi evidente nas DFs. Nos FOCs, foi possível evidenciar a descontinuidade da lesão com a cortical óssea de revestimento externo e a presença de estruturas semelhante ao cemento. Em conclusão, o diagnóstico de DF e FOC deve ser realizado a partir da correlação das características clínicas, imaginológicas e histopatológicas. No entanto, foi possível observar algumas características peculiares em cada uma das lesões, o

que poderá auxiliar o diagnóstico e consequentemente favorecer o tratamento dos pacientes acometidos por estas patologias ósseas.

Palavras-chave: Lesões fibro-ósseas benignas, Displasia fibrosa, Fibroma ossificante central; Fendas peri-trabeculares.

ABSTRACT

Fibrous dysplasia (FD) and ossifying fibroma (OF) comprehend a group of benign fibro-osseous lesions (BFOL) which mainly affects the maxilla, mandible and craniofacial bones. They are characterized by the replacement of normal bone tissue by a matrix of fibrous connective tissue with varying degrees of mineralization. Both lesions frequently share clinical and microscopic features and the final diagnose require a combined analysis of clinical, radiologic and histological data. There might be significant cosmetic and functional impairment despite having a distinct pattern of progression and biological behavior, therefore, it is important to distinguish them from each other at the final diagnose. This research focused on the study and comparison of the demographic, clinical, imaging and microscopic aspects of patients with FD and OF, at the moment of the diagnostics. A retrospective multiinstitucional research was conducted in which there were 68 FD cases and 37 of OF. Characteristics such as gender, age and anatomic site of the tumor samples were obtained from the medical records. FDs (n=41; 60,2%) and OFs (n=24; 64,9%) were more frequently detected in female patients who were at the second or third decade of life. The maxilla was more prominently affected among the FD cases (n=38; 56%) contrasting to the prevalence of the mandible in the OF cases (n=23 62.2%). According to the radiographic aspects, FDs frequently presented as radiopaque lesions, with ill-defined limits, and OFs had well defined margins and were radiolucid. Microscopically, a continuity of the lesion with the bone cortical was evident in the FDs, as well as a separation phenomenon between the bone trabeculae and the surrounding connective tissue of the adjacent stroma. In OFs, the discontinuity of the lesion with the bone cortical was noticed, so were the presence of cement-like structures. In conclusion, the diagnose of FD and OF must be done based on the sum of the clinical, radiographic and microscopic features, although it was possible to observe a few peculiar characteristics in each one of them, which might serve as a diagnostic tool and therefore improve the treatment of the patients.

Key Words: Benign fibro-osseous lesions, Fibrous dysplasia, Central ossifying fibroma.

SUMÁRIO

INTRODUÇÃO

As lesões fibro-ósseas benignas (LFOBs) compreendem um grupo de lesões que afetam principalmente a maxila, a mandíbula e ossos da região craniofacial. Caracterizam-se pela substituição do tecido ósseo normal por uma matriz de tecido conjuntivo fibroso com níveis variados de material mineralizado (MacDonald-Jankowski, 2004; Speight, Carlos, 2006; Pimenta et al., 2006; Toyosawa et al., 2007; Eversole et al., 2008; Worawongvasu, Songkampol, 2010). Fazem parte deste grupo de lesões, a displasia fibrosa (DF), o fibroma ossificante cental (FOC) e um grupo heterogêneo de lesões reativas, as displasias ósseas (Speight, Carlos, 2006; Pimenta et al., 2006; Eversole et al., 2008; Patel et al., 2011).

As classificações e terminologias utilizadas para caracterizar as LFOBs vêm sofrendo significativas alterações durante os últimos anos. Entre os anos de 1940 e 1950 estas lesões foram designadas como osteítes fibrosas localizadas, osteofibromas ou fibrosteomas e esta terminologia foi utilizada durante diversos anos (Waldron, 1993). Em 1992 a Organização Mundial da Saúde (OMS) sugeriu uma nova classificação para as LFOBs incluindo os termos DF, displasia cemento-óssea (periapical, focal e florida) e neoplasias fibro-ósseas (fibroma cemento-ossificante ou fibroma cementificante). Mais recentemente, no ano de 2005, a OMS passou a classificar as LFOBs em DF (monostótica, poliostótica e craniofacial), displasia óssea (periapical, focal e florida) e fibroma ossificante (convencional, juvenil trabecular e juvenil psamomatóide), sugerindo que o termo fibroma ossificante seria mais adequado do que o termo “cemento-ossificante”, considerando equivocada a diferenciação anteriormente realizada entre osso e cemento.

A terminologia DF foi sugerida pela primeira vez por Lichtenstein e Jaffe em duas publicações em 1938 e 1942. A incidência e prevalência da DF são difíceis de estabelecer, mas são consideradas lesões comuns, representando aproximadamente 5% das lesões benignas que acometem o osso (Dorfman 2010).

A DF é uma alteração genética de desenvolvimento do esqueleto causada por uma mutação somática no códon 201 da subunidade- α da proteína G (Gs-α) codificada pelo gene GNAS que afeta diretamente a proliferação e diferenciação dos pré-osteoblastos (Toyosawa et al., 2007; Eversole et al., 2008; Liang et al., 2011). Em mais de 80% dos casos, a DF afeta apenas um osso (monostótica), mas também pode afetar múltiplos ossos (poliostótica) e estar acompanhada de pigmentações café com leite em pele. Aproximadamente 3% das DF poliostóticas estão associadas a uma variedade de distúrbios endócrinos que acometem mulheres em fase de puberdade, a Síndrome de McCune-Albright (Waldron, 1993; MacDonald-Jankowski, 2004; OMS, 2005; Speight, Carlos, 2006). Quando a DF acomete maxila, mandíbula e ossos adjacentes como zigomático, esfenóide, ossos fronto-nasais e ossos da base do crânio passa a ser denominada DF craniofacial (Waldron, 1993; OMS, 2005; Speight, Carlos, 2006).

Clinicamente, A DF apresenta-se como uma expansão óssea assintomática que pode causar assimetria facial e que quando envolve mandíbula, maxila ou outros ossos da face, pode levar a alterações dentárias como mal oclusões e, mais raramente reabsorções radiculares. A DF geralmente é diagnosticada em crianças ou adultos jovens sendo caracterizada por uma imagem radiopaca, com margens mal delimitadas, com o aspecto semelhante ao descrito na literatura como “vidro despolido” (Waldron, 1993; Ogunsalu et al., 2001; OMS, 2005; Speight, Carlos, 2006).

Com relação ao tratamento e prognóstico, em muitos casos estas lesões estabilizam-se com a maturação esquelética, no entanto, intervenções cirúrgicas podem ser necessárias para se restabelecer a estética ou função (OMS, 2005; Toyosawa et al., 2007).

O FOC é definido pela OMS como uma neoplasia benigna que se apresenta como uma lesão bem delimitada e ocasionalmente encapsulada, o tecido conjuntivo que forma a lesão é constituído por uma quantidade variada de material mineralizado que se assemelha a osso ou a cemento (Waldron, 1993; OMS, 2005; Ono et al., 2007). De forma geral, o FOC apresenta-se clinicamente como uma

expansão óssea de crescimento lento, com elevada predileção pela região posterior de mandíbula em áreas próximas a elementos dentais, sendo diagnosticado mais frequentemente em pacientes entre a terceira e quarta décadas de vida, com maior incidência no gênero feminino (Waldron, 1993; Speight, Carlos, 2006).

Os aspectos imaginológicos do FOC geralmente evidenciam uma área radiolúcida bem circunscrita, com variáveis níveis de calcificação, podendo exibir áreas radiopacas no interior da lesão (MacDonald-Jankowski, 2004). Estas lesões tendem a mostrar crescimento progressivo enquanto permanecem sem tratamento. O tratamento de escolha para FOCs é a ressecção cirúrgica completa da lesão, sendo as taxas de recorrências em torno de 30 a 50% (OMS, 2005; Twoyosawa et al., 2007).

Embora tenham ocorrido avanços no entendimento destas lesões, o diagnóstico e o tratamento continuam apresentando limitações principalmente pela falta de concordância nos critérios de classificação e também pela importante sobreposição de aspectos clínicos e histológicos (Waldron, 1993; Speight, Carlos, 2006).

Frequentemente, as DFs e os FOCs apresentam características clínicas e histopatológicas similares e o diagnóstico final depende da correlação das características clínicas, imaginológicas e microscópicas (Speight, Carlos, 2006; Pimenta et al., 2006). DFs e FOCs podem estar associados a significantes alterações funcionais e cosméticas a despeito de possuírem um distinto padrão de progressão e comportamento biológico, portanto é muito importante fazer a distinção diagnóstica entre estas lesões (Speight, Carlos, 2006; Toyosawa et al., 2007; Eversole et al., 2008)

Existe uma constante busca na literatura na tentativa da distinção das DFs e FOCs, visto que possuem evolução e tratamentos distintos. Diante disso, o presente trabalho se fundamentou na perspectiva de reunir uma casuística representativa por meio de uma abordagem retrospectiva multicêntrica reunindo casos oriundos da Faculdade de Odontologia de Piracicaba – UNICAMP, do

Centro Clínico de Cabeça de Pescoço da Guatemala e da Escola de Odontologia Clínica de Sheffield, Reino Unido possibilitando assim uma melhor caracterização dos aspectos clínicos, imaginológicos e histopatológicos da DF e do FOC. A partir desta amostra estudada foi possível observar características clínicas e histopatológicas peculiares de cada umas das lesões e se estabelecer critérios que podem auxiliar na distinção entre DFs e FOCs e consequentemente se estabelecer o diagnóstico definitivo e melhor tratamento.

CAPÍTULO 1

Análise das características clínicas, imaginológicas e histológicas das displasias fibrosas e fibromas ossificantes centrais envolvendo mandíbula e maxila. Estudo multicêntrico internacional.

RESUMO

A Displasia Fibrosa (DF) e o Fibroma Ossificante Central (FOC) são lesões fibro-ósseas benignas caracterizadas pela substituição do tecido ósseo normal por uma matriz de tecido fibroso. Frequentemente, DFs e FOCs apresentam características clínicas e histopatológicas semelhantes, entretanto, possuem cursos clínicos distintos, fato que torna a diferenciação histológica entre estas lesões essencial. Este trabalho teve como objetivo avaliar e comparar as características clínico-patológicas de DFs e FOCs de maxila e mandíbula. Foi realizada uma análise retrospectiva internacional multi-institucional e selecionados 68 casos de DF e 37 casos de FOC. O gênero feminino foi o mais acometido tanto nos pacientes diagnosticados com DF (60,2%) quanto nos pacientes diagnosticados com FOC (64,9%). As DFs acometeram preferencialmente a maxila (56%) e os FOCs a mandíbula (62,2%). Com relação aos aspectos imaginológicos, as DFs apresentaram-se frequentemente como lesões radiopacas com limites mal definidos e os FOCs como lesões radiolúcidas bem delimitadas. Microscopicamente, foi possível evidenciar nas DFs a continuidade da lesão com a cortical óssea de revestimento e um fenômeno de separação entre as trabéculas ósseas e o tecido conjuntivo do estroma adjacente. Com relação aos FOCs, foi possível evidenciar a descontinuidade da lesão com a cortical óssea de revestimento externo e a presença de estruturas semelhante ao cemento. Em conclusão, o diagnóstico de DF e FOC deve ser realizado a partir da correlação das características clínicas, imaginológicas e histopatológicas, no entanto, foi possível observar algumas características peculiares em cada uma das lesões, o

que poderá auxiliar o diagnóstico e consequentemente favorecer o tratamento dos pacientes acometidos por estas patologias ósseas.

Palavras-chave: Lesões fibro-ósseas benignas, Displasia fibrosa, Fibroma ossificante central.

INTRODUÇÃO

As lesões fibro-ósseas benignas compreendem um grupo de lesões que afetam principalmente maxila, mandíbula e os ossos da região craniofacial. Caracterizam-se pela substituição do tecido ósseo por uma matriz de tecido conjuntivo com níveis variados de material mineralizado (MacDonald-Jankowski, 2004; Speight, Carlos, 2006; Pimenta et al., 2006; Toyosawa et al., 2007; Eversole et al., 2008; Ribeiro et al., 2011). Este grupo inclui a displasia fibrosa (DF), neoplasias benignas como o fibroma ossificante cental (FOC) e um grupo heterogêneo de lesões reativas, as displasias ósseas. Frequentemente, as DFs e os FOCs apresentam características clínicas e histopatológicas similares e o diagnóstico final depende da correlação das características clínicas, imaginológicas e microscópicas (Speight, Carlos, 2006; Pimenta et al., 2006).

Existe uma constante busca na literatura na tentativa de aprimorar a distinção destas lesões, visto que possuem evolução e tratamentos distintos. Diante disso, este trabalho se fundamentou na perspectiva de reunir uma casuística representativa por meio de uma abordagem retrospectiva multicêntrica e internacional, reunindo casos oriundos da Faculdade de Odontologia de Piracicaba – UNICAMP, do Centro Clínico de Cabeça de Pescoço da Guatemala e da Escola de Odontologia Clínica da Universidade de Sheffield, Inglaterra, objetivando assim uma melhor representatividade das características clínicas, imaginológicas e histopatológicas destas lesões. A partir dos resultados obtidos, foi possível estabelecer um perfil comparativo clínico-patológico entre DFs e FOC.

MATERIAL E MÉTODOS

Previamente a realização deste estudo houve aprovação do Comitê de Ética em Pesquisa da Faculdade de Odontologia de Piracicaba – UNICAMP

(protocolo 58/2008) e pelo Comitê de Ética e Pesquisa de Sheffield, Universidade de Sheffield (protocolo STH 15699).

Foi realizada uma análise retrospectiva dos arquivos dos serviços de patologia oral da Faculdade de Odontologia de Piracicaba, FOP-UNICAMP, Piracicaba, São Paulo, Brasil, do Centro Clínico de Cabeça de Pescoço da Guatemala, Cidade da Guatemala, Guatemala e Escola de Odontologia Clínica da Universidade de Sheffield, Inglaterra, e foram selecionados os casos com diagnóstico histológico de DF e FOC. A partir dos registros laboratoriais e prontuários dos casos selecionados foram coletados os seguintes dados: gênero, idade e localização da lesão. As características radiográficas foram coletadas a partir das fichas clínicas e quando possível foram analisados e registrados por meio de fotografia digital, permitindo assim a análise do padrão imaginológico.

RESULTADOS

Características demográficas, clínicas e radiográficas

A Tabela 1 resume os achados clínicos da amostra. A Figura 1 ilustra os aspectos clínicos mais representativos que foram observados nos pacientes com DF e a Figura 2 demonstra os aspectos imaginológicos mais frequentemente observados nos pacientes com DFs. A Figura 3 ilustra os aspectos clínicos mais observados no FOC e a Figura 4 exibe os aspectos imaginológicos predominantes encontrados nos casos FOCs.

A Tabela 2 resume os achados imaginológicos das LFOBs.

Tabela 1. Aspectos clínicos da amostra estudada.

Variáveis	DF (n=68)	FOC (n=37)
Gênero		
Feminino	41 (60,2%)	24 (64,9%)
Masculino	27 (39,8%)	13 (35,1%)
Idade no momento do diagnóstico		
1.ª década de vida (0-9 anos)	12 (17,7%)	1 (2,7%)
2.ª década de vida (10-19 anos)	22 (32,3%)	12 (32,5%)
3.ª década de vida (20-39 anos)	25 (36,7%)	14 (37,8%)
4.ª década de vida (40-49 anos)	6 (8,8%)	6 (16,2%)
5.ª década de vida (50-59 anos)	0	3 (8,1%)
6.ª década de vida (60-69 anos)	1(1,5%)	1 (2,7%)
Não especificada	2 (3%)	0
Localização Anatômica		
Mandíbula	30 (44%)	23 (62,2%)
Maxila	38 (56%)	14 (37,8%)

DF: Displasia fibrosa; FOC: Fibroma ossificante central.

Figura 1. Displasia fibrosa (CASO 42, paciente do gênero feminino, 21 anos de idade). **A.** Aspecto clínico extra-bucal evidenciando aumento de volume na região zigomática do lado direito. **B.** Aspecto clínico intra-bucal mostrando expansão óssea em maxila posterior do lado direito, envolvendo região vestibular e palatina.

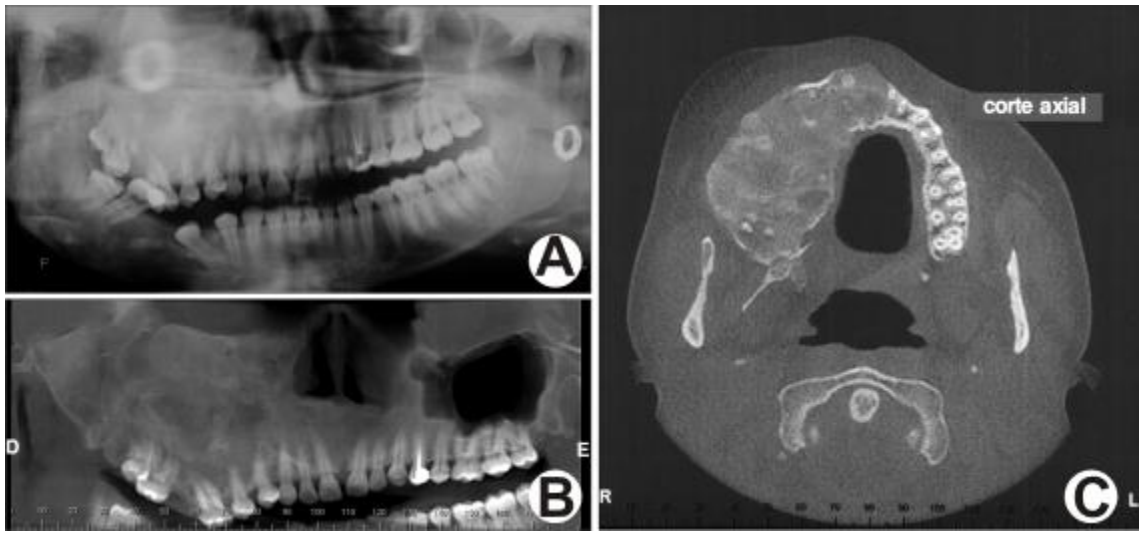

Figura 2. Displasia fibrosa (CASO 42, paciente do sexo feminino, 21 anos de idade). **A.** Radiografia panorâmica. Lesão radiopaca com limites mal definidos em região posterior de maxila do lado direito. **B.** Reconstrução panorâmica de tomografia computadorizada por feixe cônico mostrando extensa lesão envolvendo maxila posterior, seio maxilar e osso zigomático. **C.** Corte axial de tomografia computadorizada por feixe cônico exibindo aspecto homogêneo hiperdenso, descrito como “vidro despolido”. Nota-se ainda expansão da cortical óssea vestibular e palatina.

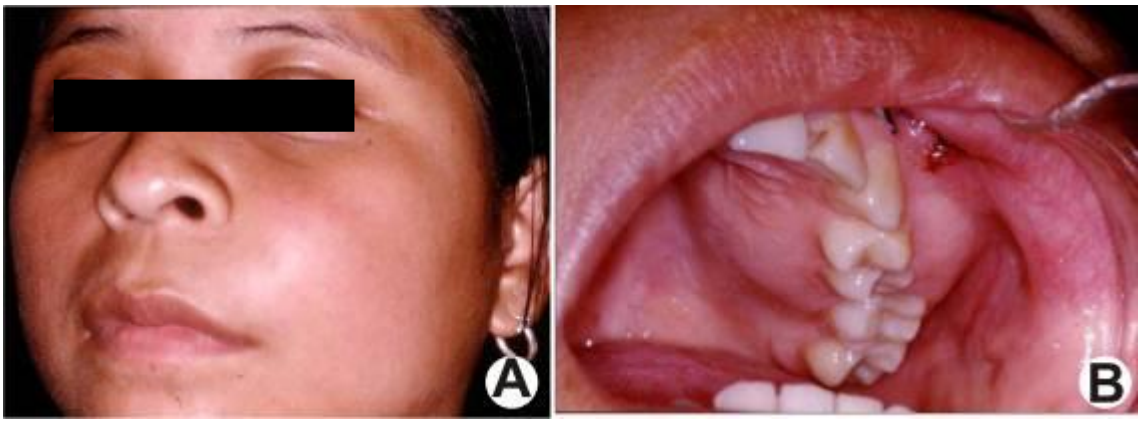

Figura 3. Fibroma ossificante central (CASO 9, paciente do gênero feminino, 18 anos de idade). **A.** Aspecto clínico extra-bucal evidenciando aumento de volume na região zigomática do lado esquerdo. **B.** Aspecto clínico intra-bucal mostrando expansão óssea em maxila do lado esquerdo, envolvendo região vestibular e palatina.

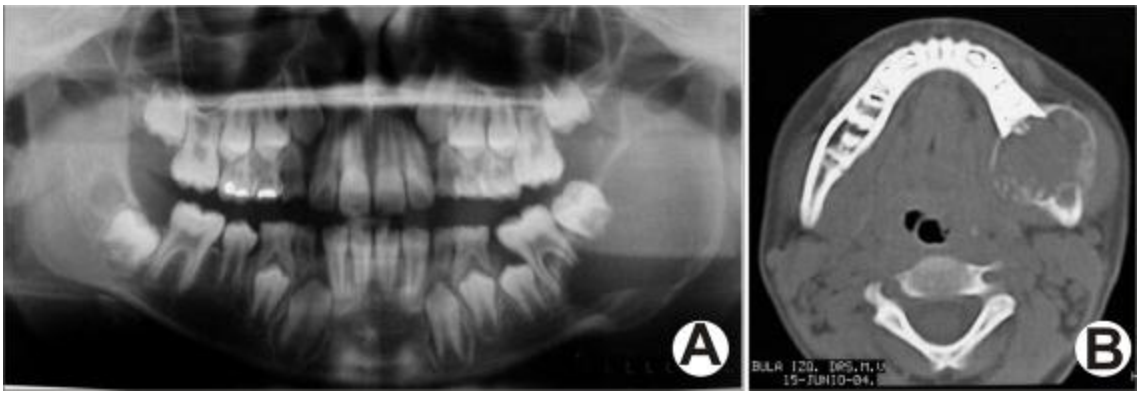

Figura 4. Fibroma ossificante central (CASO 8, paciente do gênero masculino, 9 anos de idade). A. Radiografia panorâmica. Lesão radiolúcida com limites bem definidos, mostrando abaulamento da cortical óssea inferior da mandíbula do lado esquerdo. B. Corte axial de tomografia computadorizada adquirida com janela para tecido duro evidenciando uma lesão hipodensa bem delimitada. Nota-se expansão da cortical óssea vestibular e lingual.

Tabela 2. Aspectos imaginológicos da amostra de lesões fibro-ósseas benignas.

Aspectos Imaginológicos	**DF (n=68)**	**FOC (n=37)**
Imagem Radiopaca	38 (55,6%)	2 (5,4%)
Margens mal definidas	31 (45,5%)	0
Margens bem definidas	4 (5,8%)	2 (5,4%)
Informação não disponível	3 (4,3%)	0
Imagem Mista (radiopaca/radiolúcida)		
Margens mal definidas	1 (1,5%)	4 (10,5%)
Margens bem definidas	5 (7,4%)	11 (29,7%)
Informação não disponível	3 (4,3%)	0
Imagem Radiolúcida		
Margens mal definidas	2 (3%)	0
Margens bem definidas	2 (3%)	12 (32,5%)
Informação não disponível	0	3 (7,9%)
Desconhecidos	17 (25,3%)	5 (13,5%)

Características histopatológicas

Histologicamente, a DF se caracterizou pela substituição do tecido ósseo normal por tecido conjuntivo fibroso. Em 49 (72%) casos foi possível observar a presença da cortical óssea de revestimento na biópsia analisada, destes, 100% apresentaram continuidade da lesão com a cortical óssea de revestimento como pode ser observado na Figura 5. As trabéculas ósseas lesionais mostraram uma distribuição simétrica por toda a extensão da lesão em todos os casos analisados, mostrando uma evidente homogeneidade em sua distribuição, como se o padrão de distribuição das trabéculas ósseas se repetisse por toda a extensão da lesão (Figura 6). Em 15 (22%) casos da amostra foi possível observar escassas estruturas calcificadas, semelhantes a cemento.

Foram observadas características distintas nas diferentes fases de maturação das lesões, sendo que 63 (92,6%) amostras foram classificadas histologicamente como maduras (Figuras 6A, 6B, 6C e 6D) e 5 (7,4%) como imaturas (Figura 7). O estroma das DFs imaturas apresentou uma celularidade mais elevada quando comparado às lesões maduras, onde se observou um padrão celular mais monótono, de baixa celularidade.

Outro aspecto que foi evidenciado durante a análise das DFs foi um fenômeno de separação entre as trabéculas ósseas lesionais e o tecido conjuntivo adjacente, mostrando um espaço negativo entre o osso e o estroma fibroso circunjacente (Figura 6 D). Em todas as amostras que apresentavam um maior grau de maturação, este fenômeno foi evidente, enquanto que nas amostras classificadas como imaturas, foi observado apenas um discreto espaço negativo entre o osso e o tecido fibroso circunjacente ou ausência deste fenômeno.

A presença de células gigantes multinucleadas tipo osteoclasto foi observada em 5 (7,4%) casos da amostra, sendo que 4 destas lesões foram classificadas histologicamente como DFs imaturas (Figura 7).

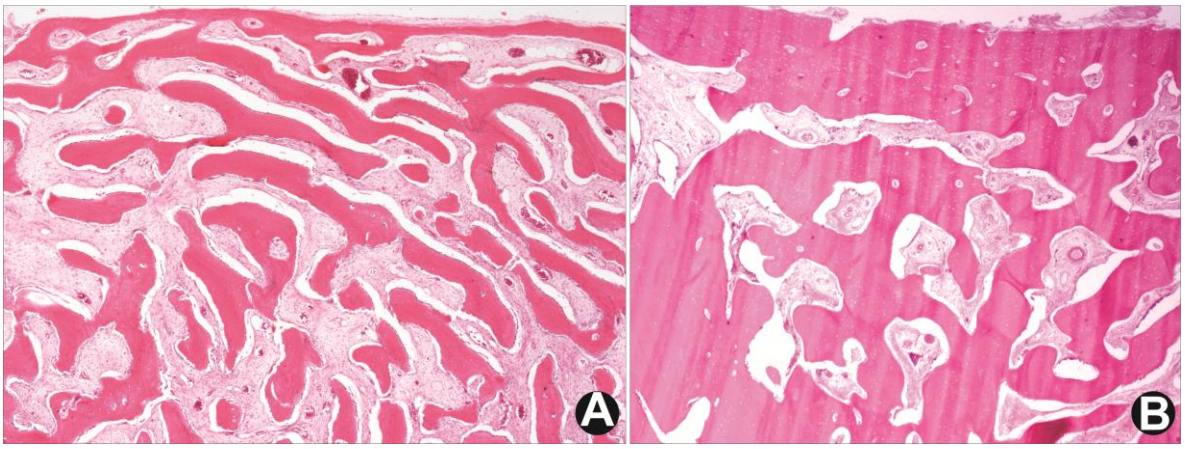

Figura 5. Displasia fibrosa. **A.** Fotomicrografia evidenciando continuidade da lesão com a cortical óssea externa e o paralelismo na distribuição das tabéculas ósseas lesionais (HE 40X). **B.** Detalhe da continuidade da lesão com a cortical óssea de revestimento (HE 50X).

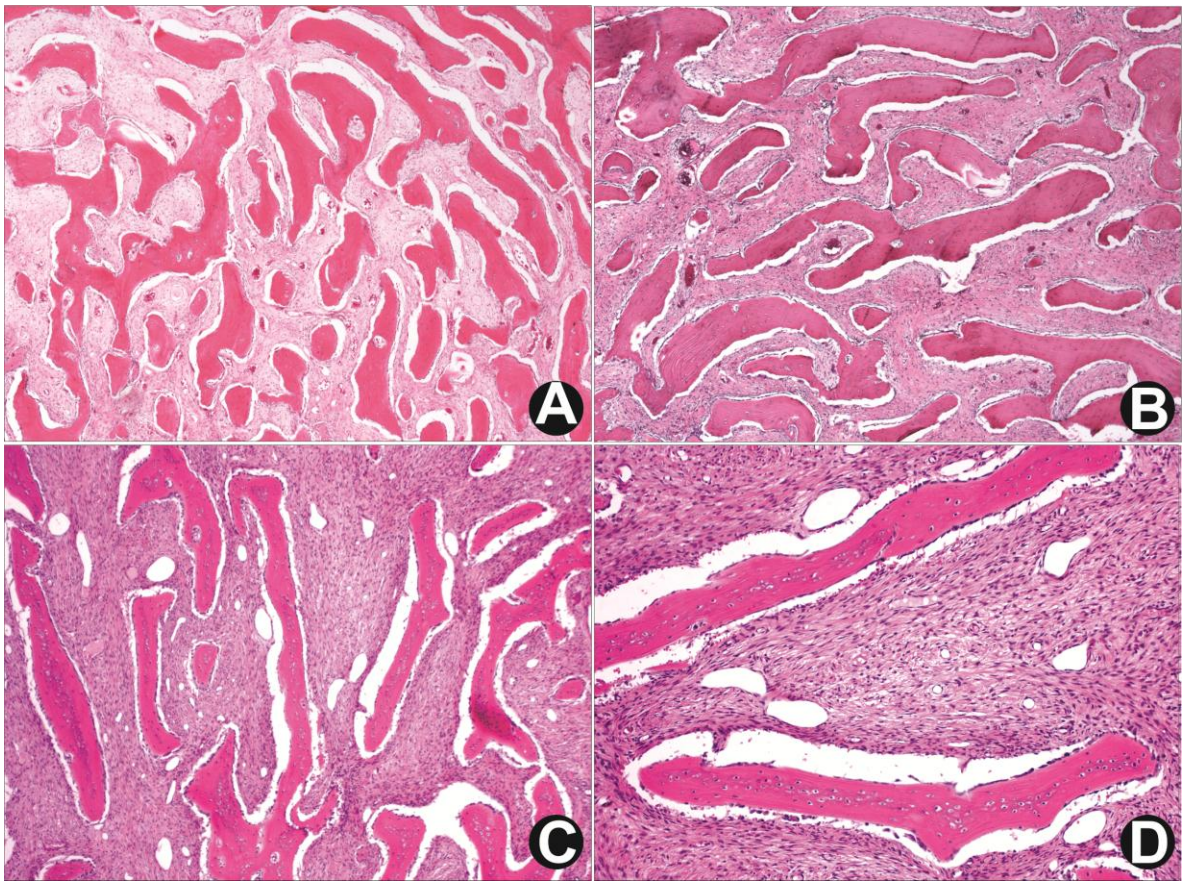

Figura 6. Displasia fibrosa madura. **A.** Trabéculas ósseas mostrando distribuição homogênea por todo o campo avaliado (HE 40X). **B.** Fenômeno de separação entre as trabéculas e tecido conjuntivo (HE 40X). **C.** Evidente paralelismo entre as trabéculas ósseas da lesão (HE 50X). **D.** Detalhe do fenômeno de separação entre as trabéculas ósseas e o tecido conjuntivo adjacente (HE 100X).

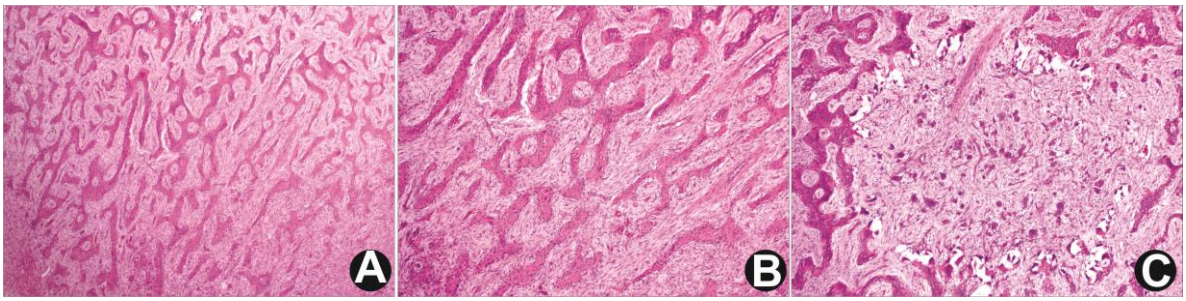

Figura 7. Displasia fibrosa imatura **A.** Trabéculas ósseas lesionais mostrando distribuição homogênea por todo o campo avaliado (HE 25X). **B.** Padrão de distribuição homogêneo das trabéculas ósseas lesionais que são semelhantes entre si (HE 50X). **C.** Presença de células gigantes multinucleadas tipo osteoclastos distribuídas no estroma da lesão (HE 100X).

Em todas as amostras de FOCs onde foi possível observar cortical óssea de revestimento (54%), foi observada descontinuidade total da lesão com a cortical óssea. As trabéculas ósseas lesionais mostraram uma distribuição heterogênea em todos os casos da amostra, distribuindo-se aleatoriamente por toda a extensão da lesão (Figura 8).

Todos os casos de FO apresentaram um estroma com uma celularidade alta (Figura 9). Em todos os casos avaliados notou-se variada quantidade de estruturas arredondadas, calcificadas, semelhantes a cemento, que foram observados em toda a extensão das lesões (Figuras 8 e 9). Foi possível evidenciar em 76,2% da amostra de FO que as lesões se apresentaram bem delimitadas com presença de cápsula fibrosa circunscrevendo toda a lesão (Figura 9). A presença do fenômeno de separação das trabéculas ósseas lesionais do tecido conjuntivo, bem como a presença de células gigantes multinucleadas não foi observada em nenhum caso de FOC da amostra estudada.

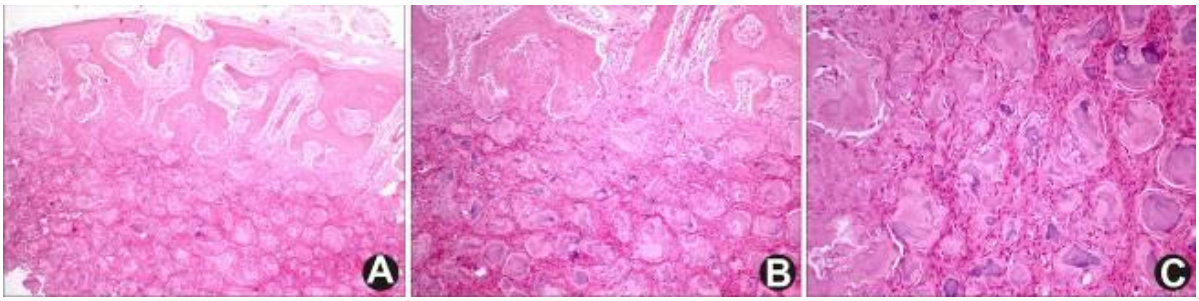

Figura 8. Fibroma ossificante central. **A.** Fotomicrografia mostrando a completa descontinuidade da lesão com a cortical de revestimento (HE 50X). **B.** Detalhe da descontinuidade da lesão com a cortical óssea externa e presença de material calcificado no estroma lesional (HE 100X). **C.** Detalhe das estruturas arredondadas e calcificadas semelhantes a cemento (HE 200X).

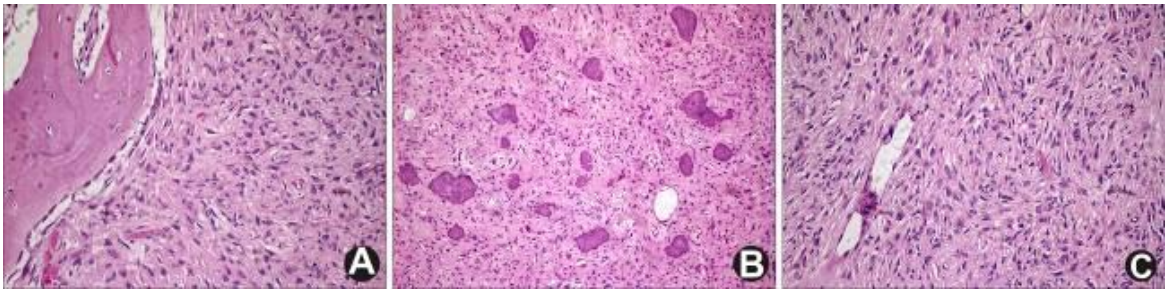

Figura 9. Fibroma ossificante central. **A.** Fotomicrografia mostrando a completa descontinuidade da lesão com a cortical óssea de revestimento e presença de cápsula fibrosa (HE 100X). **B.** Evidenciação de estruturas calcificadas semelhantes a cemento e baixa vascularização da lesão (HE 200X). **C.** Estroma mostrando celularidade alta e variada, fibroblastos com núcleos arredondados e pouca quantidade de vasos sanguíneos (HE 200X).

DISCUSSÃO

As lesões fibro-ósseas benignas compreendem um grupo de patologias que afetam principalmente os ossos da região craniofacial sendo caracterizadas pela substituição do tecido ósseo normal por uma matriz de tecido conjuntivo fibroso

com focos de mineralização. DF e FO frequentemente apresentam um dilema diagnóstico por apresentarem aspectos clínicos, imaginológicos e histopatológicos similares (MacDonald-Jankowski, 2004; Barnes et al., 2005; Speight, Carlos, 2006; Pimenta et al, 2006; Toyosawa et al, 2007; Eversole et al, 2008; Alsharif et al, 2009). Embora estas lesões possuam similaridades, o diagnóstico definitivo é de fundamental importância visto que cada uma possui comportamento clínico e tratamento distintos (Patel et al, 2010).

O presente trabalho reuniu uma casuística multicêntrica representativa com 68 (64,76%) pacientes diagnosticados com DF e 37 (35,24%) diagnosticados com FOC. A partir desta amostra estudada foi possível observar características clínicas e histopatológicas peculiares de cada umas das lesões, o que pode ser auxiliar no diagnóstico definitivo.

Na amostra estudada a média de idade dos pacientes diagnosticados com DF foi 20,7 anos e dos pacientes diagnosticados com FOC foi de 30,25 anos. O gênero feminino foi o mais acometido nos pacientes diagnosticados com DF (n=41; 60,2%) e FOC (n=24; 64,9%). As DFs acometeram preferencialmente a maxila (n=38; 56%) e os FOC a mandíbula (n=23; 62,2%). Estes achados são similares aos observados por Worawongvasu, Songkampol (2010) que analisaram uma amostra constituída de 62 casos de FOCs e 52 DFs. Os resultados mostraram uma maior incidência de FOCs em mulheres (87,1%) com igual distribuição na segunda e terceira (30,6%) década de vida e uma maior incidência de casos acometendo a mandíbula (79%). A amostra de DF mostrou uma maior incidência em pacientes do gênero feminino (71,2%), um pico de incidência na primeira década de vida e com maior ocorrência em maxila (53,4%) quando comparada a mandíbula (46,6%).

O presente trabalho demonstrou que pode haver uma variação nos aspectos radiográficos das DFs e FOCs. No entanto, em concordância com os trabalhos de Speight, Carlos (2006) e Eversole (2009), a amostra em questão identificou que as DFs se apresentaram predominantemente como lesões radiopacas (45,5%), com margens mal delimitadas, de aspecto semelhante ao

descrito na literatura como “vidro despolido”. Dos casos de FOC, 40,4% se caracterizaram como imagens radiolúcidas, destes, 32,5% apresentaram margens bem delimitadas.

Speight, Carlos (2006) descreveram algumas características histopatológicas que poderiam auxiliar na distinção entre a DF e FOC, características estas que corroboram com nossos achados como a presença de cortical óssea de revestimento em continuidade da lesão em 72% das amostras de DF e descontinuidade em 54% das amostras de FOC. Outro aspecto morfológico evidenciado nos casos de DFs foi à presença de um paralelismo na distribuição das trabéculas, padrão que não foi evidenciando nos FOCs.

Um padrão morfológico bastante importante que foi observado e não há relatos prévios na literatura foi à presença de um fenômeno de separação entre as trabéculas ósseas e o tecido conjuntivo adjacente nas DFs, mostrando um espaço negativo entre o osso e o tecido fibroso circunjacente, característica que pode ser uma importante ferramenta diagnóstica histopatológica na diferenciação entre as DFs e os FOCs.

Considerações finais

Quando os dados da literatura relacionados às LFOBs são estudados, as divergências ficam claras e têm início no critério utilizado para se definir a terminologia das lesões incluídas neste grupo, bem como na identificação de características clínicas, imaginológicas, microscópicas e, mais recentemente, moleculares, que poderiam auxiliar na identificação e diagnóstico definitivo destas lesões, visto que possuem evolução e tratamentos distintos. A partir de uma análise retrospectiva multicêntrica reunindo casos oriundos da Faculdade de Odontologia de Piracicaba – UNICAMP, do Centro Clínico de Cabeça de Pescoço da Guatemala e da Escola de Odontologia Clínica da Universidade de Sheffield, Inglaterra, o presente estudo agrupou uma casuística representativa e, consequentemente, promoveu uma melhor caracterização dos aspectos clínicos,

imaginológicos e histopatológicos das DFs e do FOCs. Fato que possibilitou o reconhecimento de aspectos clínico-patológicos peculiares que podem auxiliar os patologistas orais na distinção entre estas duas lesões, o que poderá ser observado no decorrer dos capítulos deste trabalho de tese.

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CAPÍTULO 2

Artigo submetido para publicação no periódico *Histopathology.*

Peritrabecular clefting in fibrous dysplasia of the jaws: an important histopathological feature for differentiating fibrous dysplasia from central ossifying fibroma

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Peritrabecular clefting in fibrous dysplasia of the jaws: an important histopathological feature for differentiating fibrous dysplasia from central ossifying fibroma

ABSTRACT

The differentiation of fibrous dysplasia (FD) from other fibro-osseous lesions (FOLs) can be difficult, especially in the case of ossifying fibroma (OF), because they can present similar clinical, histopathological and imaging features. Such lesions must be distinguished because they have distinct outcomes and require different forms of treatment. The aim of this international multi-centre study was to perform a histomorphometric analysis of peritrabecular clefting in FD in an attempt to obtain data that could be useful for distinguishing between FD and OF. A clinicopathological analysis was performed in 68 patients diagnosed with FD and 37 patients diagnosed with OF. Histological sections were scanned using an Aperio ScanScope® CS and images of representative areas of the tumours were taken using ImageScopeTM software. A histomorphometric analysis was performed with the aid of an image analyser (UTHSCSA Image Tool 3.0 version) on 38 randomly selected samples of FD and the results were compared with the 37 OF specimens. The presence of peritrabecular clefting was observed in 33 (86.8%) cases of FD, whereas no case of OF presented peritrabecular clefting. The mean area of the clefts obtained from manual measurements was 6733.11 μm2. In conclusion, peritrabecular clefting was a hallmark in the FD patients, and it may be an important microscopic feature for distinguishing it from OF. Thus, the authors would like to add this potentially important microscopic feature to the clinicopathological correlations necessary for the final diagnosis of FD.

Keywords: Benign fibro-osseous lesions, Fibrous dysplasia, Central ossifying fibroma, Histomorphometric analysis, Digital pathology.

INTRODUCTION

Benign fibro-osseous lesions (FOLs) are a group of lesions that affect the jaws and craniofacial bones in which normal bone is replaced by cellular fibrous tissue with different degrees of mineralized material[1-4]. This group of bone diseases encompasses fibrous dysplasia (FD), central ossifying fibroma (OF) and osseous dysplasia[1,2].

The World Health Organization currently defines FD as a genetically based sporadic disease of the bone that may affect single or multiple bones (monostotic and polyostotic types, respectively) and when it occurs in different craniofacial bones it is regarded as craniofacial FD. Central ossifying fibroma (OF) is a benign neoplasm that often presents well-demarcated borders and is histologically composed of fibrocellular stroma and variable amounts of mineralized material[5]. Fibrous dysplasia and OF often present clinical, histopathological and imaging similarities and a definitive diagnosis requires a precise clinicopathological correlation. These lesions must be distinguished from each other because they have distinct outcomes and require different forms of treatment.

Peritrabecular clefting has been previously illustrated in a number of publications, but no studies have been undertaken to determine if this feature is specific to fibrous dysplasia, or if it may be a useful diagnostic marker [Speight and Carlos (2006; Figures 1 and 3)[1], Eversole et al. (2008; Figure 3A)[3] and Slootweg (2009; Figure 21)[15]].

Therefore, the aim of the present study was to perform a descriptive analysis of peritrabecular clefting in FD and to further analyse this clefting phenomena through a histomorphometric study. In addition the prevalence and extent of clefting in FD was compared to lesions of OF.

PATIENTS AND METHODS

A retrospective, multi-centre, international, collaborative study was performed in three oral pathology centres: University of Campinas, Piracicaba Dental School, Brazil; Centro Clínico de Cabeza y Cuello, Guatemala and The University of Sheffield, United Kingdom. Demographic data (age and gender) and site of the tumours were collected from patient charts. Tissue specimens were retrieved from all patients diagnosed with FD and OF of the jaw.

This study was approved by the Ethics Committee for Human Studies, Piracicaba Dental School, University of Campinas (58/2008) and the South Sheffield Research Ethics Committee, University of Sheffield (STH 15699).

Histopathological analysis

After specimen selection, 5 µm-thick sections were cut from the selected paraffin blocks, stained with haematoxylin and eosin (H&E) and re-examined under light microscopy for diagnostic confirmation. All slides were scanned using an Aperio ScanScope® CS (Aperio Technologies Inc., Vista, CA, US) (20X magnification) and images of representative areas of the tumours were taken from each slide using the ImageScopeTM software (Aperio Technologies Inc., Vista, CA, US) (200X magnification).

The histomorphometric analysis was performed with the aid of an image analyser UTHSCSA Image Tool (IT) version 3.0 (University of Texas Health Science Center, San Antonio, Texas, US). The parameters analysed included the area of negative space between the trabecular bone and the stroma of the lesions (50X magnification). This was obtained by manually measuring the contours of the negative area with the adjustable line of the image analyser. After the system was calibrated, measurements were performed true to scale in the free-hand mode (Figure 1). All measurements were analysed in five randomly selected different

microscopic fields and these data were used to calculate the mean value for each sample. The images taken from FD and OF patients were compared further.

RESULTS

Clinical features

A group of 68 patients diagnosed with FD and 37 patients diagnosed with OF were studied. Their clinicopathological features are summarized in Table 1. From the 68 samples of FD, 38 cases were randomly selected for histomorphometric analyses and compared with all 37 cases of OF.

Histomorphometric analysis

Peritrabecular clefting was observed in 33 (86.8%) cases of FD; however, this feature was not observed in any of the OF cases (Figure 2). These clefts were characterized by a negative space between the trabecular bone and stroma of the lesions (Figure 3A, 3B, 3C and 3D). The size, shape and area of the clefts varied between the FD lesions, and the mean area obtained by manual measurement was 6733.11 μm^2, ranging from 732.37 μm^2 to 37292.79 μm^2, with an amplitude of 36560.42 μm^2.

DISCUSSION

Fibrous dysplasia and OF are the most common types of FOLs and, because of their overlapping clinical, radiographic and histopathologic features, a definitive diagnosis requires a complete correlation between clinical, histopathologic, and imaging findings[1-5,10]. The clinicopathological findings of the FOLs detected in the current study were in accordance with those in earlier studies[1,3,12].

Several diagnostic criteria have been proposed to distinguish between FOLs, but only a minority of these features are truly specific and used during routine oral pathology. Waldron (1993)[10], Speight and Carlos (2006)[1] and Eversole et al. (2008)[3] described the clinical, radiographic and histopathological features of FD and OF in an attempt to differentiate these lesions and, more recently, other authors have tried to find immunohistochemical and molecular differences between such lesions[11,13,14]. Despite these efforts to characterize and differentiate FOLs, the understanding of these conditions is still very limited.

In the current study, a histomorphometric analysis was performed in an attempt to quantify the extent of peritrabecular clefting in FD, which was observed in 86.8% of the samples. The mean area of peritrabecular clefting was 6733.11 μm^2 and a large variation in the area of the clefts and consequently a large amplitude were observed, which could be explained by the high variability in the trabecular bone size and the shape around the negative spaces (clefts).

This clefting phenomena was absent in only five (13.2%) out of 38 FD cases. Interestingly, three of these five cases in which clefting was not observed affected very young patients and their lesions presented unusual features on radiology. These lesions were histologically characterized by an immature FD pattern.

Peritumoural clefts separating tumour cells from the adjacent stroma can frequently be seen on histological sections of different tumours, such as basal cell carcinoma, prostatic adenocarcinoma and squamous cell carcinoma of the oesophagus for which they represent well-known diagnostic criteria[6,9]. The origin of peritumoural microscopic clefting is unknown, but it may be regarded as an artefact resulting from tumour retraction occurring during routine tissue processing for the preparation of light-microscopy sections[9], or an abnormality in the expression of collagenases or some other enzymes[7]. To the best of our knowledge, this is the first report to describe peritrabecular clefting in FDs and the origin of this phenomenon remains uncertain. However, due to the large amount of clefting detected in the current FD specimens, this phenomenon cannot be ignored.

Remarkably, during the literature review process for FOLs, we observed that peritrabecular clefting was illustrated in many of the papers describing the histopathological aspects of FDs, but such findings were not recognized as important microscopical features by the authors of these papers. Representative examples of peritrabecular clefting in FD images can be found in the papers by Speigth and Carlos (2006; Figures 1 and 3)1, Eversole et al. (2008; Figure 3A)[3] and Slootweg (2009; Figure 21)[15].

In conclusion, several diagnostic criteria have previously been proposed in order to diagnose and differentiate FD from OF, but none of these criteria alone have been proven to be sufficient for distinguishing these lesions. The presence of peritrabecular clefting may be an important microscopic diagnostic feature in FD and we would like to propose this as an additional diagnostic criterion and emphasize the importance of its identification during the analysis of representative biopsies of FD.

ACKNOWLEDGEMENTS

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DISCLOSURE/DUALITY OF INTEREST

The authors have no duality of interest to declare.

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TABLE

Table 1. Clinical features of the samples

Clinical features	**DF cases n=68**	**OF cases n=37**
Mean age (years)	20.7	30.25
Gender		
Female	41 (60.2%)	24 (64.9%)
Male	27 (39.8%)	13 (35.1%)
Anatomic site		
Maxilla	38 (56%)	14 (37.8%)
Mandible	30 (44%)	23 (62.2%)

FIGURES AND LEGENDS

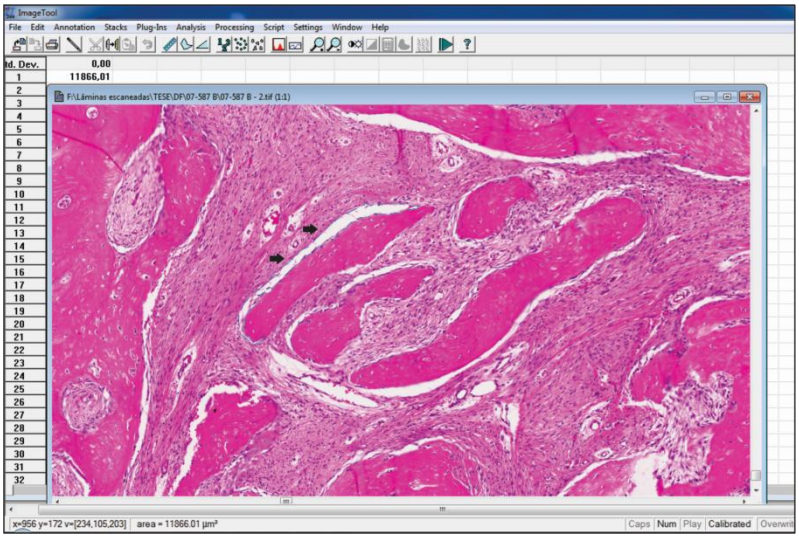

Figure 1. Histomorphometric analysis area of the peritrabecular clefting, performed using an image analyser – UTHSCSA Image Tool (IT) version 3.0.

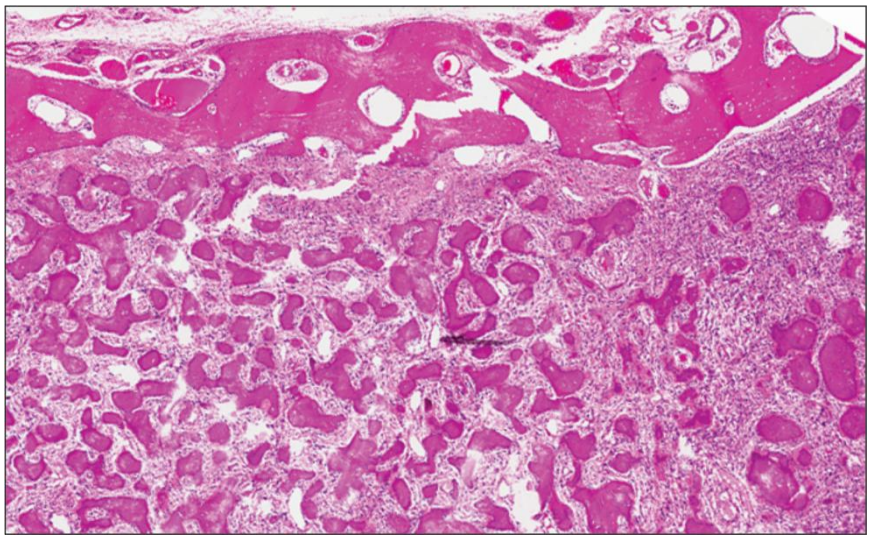

Figure 2. Ossifyng Fibroma. Histopathological features of OF, showing the absence of peritrabecular clefting (HE 20X).

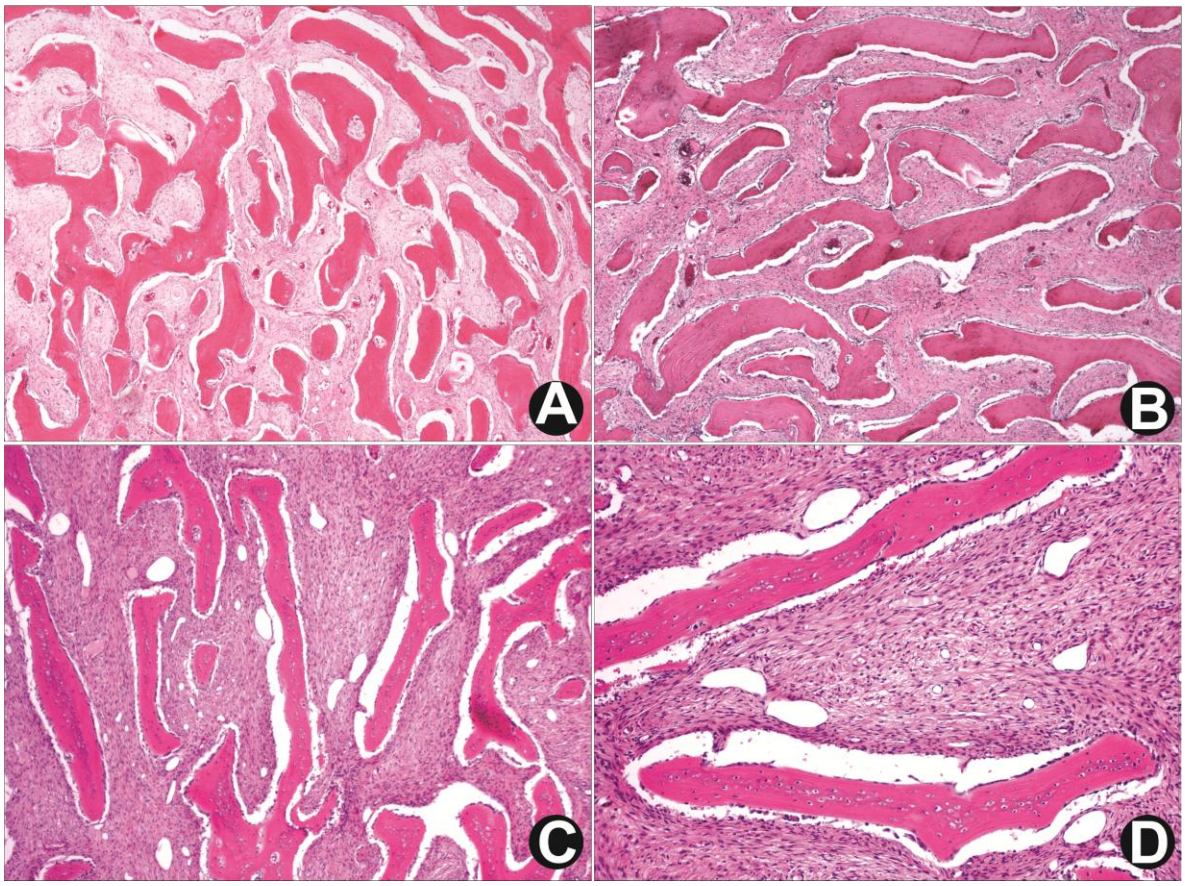

Figure 3. Fibrous dysplasia. **A and B**. Trabecular bone showing diffuse peritrabecular clefting throughout the lesion (HE 20X). **C.** Peritrabecular clefting showing different sizes and shapes (HE 100X). **D.** Detail of the peritrabecular clefting showing different sizes and shapes (HE 200X).

CAPÍTULO 3

Artigo submetido para publicação no periódico *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology.*

Immature fibrous dysplasia of the jaws: clinicopathological and immunohistochemical features of five cases.

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Immature fibrous dysplasia of the jaws: clinicopathological and immunohistochemical features of five cases.

ABSTRACT

Fibrous dysplasia (FD) is described as a developmental skeletal disorder characterized by replacement of normal bone with benign cellular fibrous connective tissue. FD was recently described as a genetic disease caused by somatic activating mutation encoded by the GNAS gene. Several authors reported the imaging features of FD according to its stage of maturation, however, histopatological aspects of this lesion according to immature its phase have never been presented. This international multi-centre collaborative study describes five cases of immature FD, presents its clinicopathological features, differential diagnosis and the osteocalcin expression of early stage FD. Three (80%) patients were females and 2 (20%) were males. The mean age at diagnosis was 11.2 years (ranging from 2 to 27 years) and the posterior mandible (80%) was the most affected site. In 3 (60%) cases, lesions presented as mixed images with well limited margins. Histologically, all cases showed pronounced woven bone production, with collagen fibers arranged in an irregular overlapping pattern. The stroma of the lesions was highly cellularized and in 4 (80%) cases a large amount of multinucleated giant cells was observed. The immunoreaction of osteocalcin showed wide positivity in osteoblasts and osteocytes. Immature FD presents distinct clinical, imaging and histopathological features. Thus, it may be misdiagnosed with other lesions that affect the jaws. The immunoreactivity found for osteocalcin might assist oral pathologists to make the precise diagnostic off immature FDs.

Keywords: Benign fibro-osseous lesions, Fibrous dysplasia, Osteocalcin.

INTRODUCTION

Fibrous dysplasia (FD) is a fibro-osseous lesion (FOL) characterized by replacement of the normal bone by cellular fibrous tissue exhibiting different degrees of mineralized material[1-4]. It may be divided into three categories: monostotic, polyostotic and craniofacial[5,6].

FD is caused by a somatic mutations at codon 201 of the alpha-subunit of G protein (Gs-alpha), encoded by the GNAS gene affecting proliferation and differentiation of preosteoblasts[3,7,8].

The imaging features of FD vary depending on the stage of maturation of the disease. Early lesions present as a radiolucent or lytic image (cystic aspect), at the intermediate phase, the lesions are described as sclerotic, and late FD shows progressively calcification, culminating in a ‘‘ground glass’’ pattern or radiolucent and radiopaque pattern[3,5,6,9].

Waldron et al. (1993)[9] depictured imaging features of the different stages of maturation of FD of the jaws. Conversely, the histopatological aspects of FDs according to its phase of maturation have never been discussed. Slootweg & Müller (1990)[10] evalued 30 cases of FOLs in order to determine histopathological parameters that could be usefull to distinguish FD from other FOLs, such authors described some important histopathological parameters of distinction, however, they did not evaluate FDs according to its variable stages of maturation. More recently, Eversole et al. (2008)[3] published their perspectives regarding the different histopathological features of FD without mentioning immature FD of the jaws.

Therefore, the purpose of this international multi-centre collaborative study was to present five cases de immature FD, to determine the relative frequency, to discuss the clinicopathological features and to provide differential diagnosis. In addition, the expression of osteocalcin, a bone formation marker, was investigated at this early stage of development.

CASES SERIES

PATIENTS AND METHODS

A retrospective review for the period from 1984 to 2009 was performed for the files of 3 oral pathology centers - University of Campinas, Piracicaba Dental School, Brazil; Centro Clínico de Cabeza y Cuello, Guatemala and University of Sheffield, School of Clinical Dentistry, United Kingdom.

Five patients diagnosed with immature FD were selected. Demographic data (age and gender) and site of the tumors were collected from the patients' charts. After specimen selection, 5-µm-thick sections were cut from the paraffin blocks, stained with haematoxylin and eosin (H&E) and re-examined under light microscopy to confirm initial diagnosis.

Exclusion criteria were insufficient tissue for analysis and lack of clinical and imaging data. This study was approved by the Ethics Committee for Human Studies, Piracicaba Dental School, University of Campinas (58/2008) and the South Sheffield Research Ethics Committee, University of Sheffield (STH 15699).

Immunohistochemistry

Streptavidin-biotin technique was employed according to the parameter of Vargas et al. (2008)[11] to carry out the immunohistochemical reactions for osteocalcin. Antigen retrieval was performed by proteinase K digestion (Code S3004; Dako, Carpinteria, CA). Sections were blocked with Protein Block Serum-Free ready-to-use (Code X0909; Dako, Carpinteria, CA). The slides were incubated with the primary anti-osteocalcin monoclonal antibody (1:200 - clone; OC4-3 - TaKaRa Biomedicals, Shiga, Japan).

RESULTS

Clinical and imaging features

The series consists of 5 cases classified as early or immature FD. Their clinicopathological features are summarized in Table 1 and in Figure 1. The mean age of the patients at the time of the biopsy was 11.2 years (with ages ranging from 2 to 27 years). The posterior mandible (80%) was more affected than the maxilla (20%).

In cases 1, 2, 3 and 5 (Figure 2A), convencional radiographics exams were available (panoramic radiography). In case 4 (Figure 2B), computerized tomography could be retrieved from patient's chart. Image features of immature FDs revealed mixed and well delimited margins in 3 cases (cases 1, 3 and 4). In 2 cases (cases 2 and 5) lesions were mainly radioluscent with well delimited margins. The mean size of immature FD lesions was 5.9 cm in the major diameter (ranging from from 1.5 to 10 cm) and the mean time of onset of lesion was 34.2 months (ranging from 3 to 70 months).

In cases 1, 3 and 4 the clinical differential diagnosis included, central ossifyng fibroma, as calcifying epithelial odontogenic tumor (Pindborg tumor) and calcifying cystic odontogenic tumor. Cases 2 and 5 which presented radiolucent and well delimited images, had as main diagnosis central ossifying fibroma and odontogenic tumors such as odontogenic keratocyst and ameloblastoma. Data regarding related sympthoms could not be found within patient's charts.

Histopathological features

All cases of immature FDs of the jaws showed pronounced woven bone production, with collagen fibers arranged in an irregular overlapping of fibers (Figure 3A). The trabeculae of woven bone was thin, small and curvilinear with

evident osteoblast rimming and a large amount of osteocytes (Figure 3B). Mature lamellar bone was not observed in any of the cases.

The stroma of the lesions was highly cellularized showing spindle-shaped fibroblastic cells in a dense fibrous tissue background. In 4 cases (cases 2, 3, 4 and 5), a large amount of multinucleated giant osteoclast-like cells adhered to the woven bone and disperse in the fibrous tissue could be observed (Figure 3C). Small and basophilic spherical calcifications (cementum-like) were observed in 1 case (case 1).

The lesional trabecular bone was observed to be in continuity with the adjacent overlying cortex bone in all cases (Figure 3D). In this early maturation stage, FD did not present peritrabeuclar clefting, a negative space between the trabecular bone and the stroma of the lesions, recently described by our group as an important finding in FD of the jaws[12].

Immunohistochemical features

Immuno reactivity for osteocalcin was observed in the cytoplasm of all bone surrounding osteoblasts and osteocytes (Figure 4A). The multinucleated giant osteoclast-like cells stained for osteocalcin in any of the cases analyzed (Figure 4B).

DISCUSSION

Waldron in 1993[9] described the different imaging features of the jaws FD. Briefly, the author classified early lesions as more radiolucent than mature lesion which presented a radiopaque pattern similar to “ground-glass”. Currently, the same classification has been applied by several authors[3,5,13]. However, the clinical and histophatological features of the so-called early or immature FD have never been described.

In the current study 5 patients presented clinical, imaging and histopathological features compatible with immature FD. The mean age of these patients was 11.2 years at diagnosis; this finding is in accordance with earlier studies that described early lesions to be more often detected during the first two decades of life[1,3,5,9].

Akintoye e al. (2004)[14] states that the appearance of FD is associated with the age of a particular lesion, rather than the age of the patient at the diagnosis. Interestingly, 2 patients (cases 1 and 5) who had more advanced age at the diagnosis showed lesions with longer times of onset (median time of onset of 5.5 years), with no prior diagnosis and treatment.

Differently from what is reported in the literature, in the current study, the mandible (80%) was more affected than the maxilla (20%). All early FD lesions presented similar image features, incluinding well-delimited margins, which is different from what is described for standart FD of the jaw. A variation between mixed (60%) and radioluscent (40%) images were frequently observed in early stages of FD, as reported by Waldron et al. (1993)[9]; Barnes et al. (2005)[5] and Eversole et al. (2008)[3]. The imaging aspects described in the present study are consisting with the histological features. The woven bone is usually generated during periods of rapid bone growtn, consequently woven bone is weaker, less rigid and more flexible than lamellar bone[15] which provides a predominatly radiolucent pattern. Histologically, the immature FD presented exclusively woven bone and hypercellular fibroblastic stroma.

Multinucleated giant osteoclast-like cells were widely observed (80% of the cases) in the present study. Similarly, Jaffe et al. (1953)[16] reported the occurrence of these cells in FD. This finding could be related to the high bone remodeling activity in immature FD of the jaws which is the simultaneous presence of areas of intense bone formation intercalated with areas of osteoclastogenesis. This, in turn, could be the basis to explain the radioluscent or mixed radiographic pattern of immature FD.

Osteocalcin is a bone-specific extracellular matrix protein that binds with calcium and can promote calcification of the matrix, it is considered to be a marker of mature osteoblasts. The abundance of osteocalcin staining in immature FD suggests that the calcified material in FD is similar to normal bone[7,17]. The consistently immunoreactivity for osteocalcin observed in the cytoplasm of bone surrounding osteoblasts found in the present study contradicts the theory that osteoblasts from early FDs are more immature, and therefore, would be unable to express osteocalcin and to promote mineralization.

Despite the homogeneous features described, clinical and imaging diagnosis of immature FDs can be difficult. The differential diagnosis should include ossifying fibroma, odontogenic tumors, odontogenic cysts among others. Most importantly of immature FD could generate over treatment and deformities in young patients.

In the current series, central ossifying fibroma was the main clinical diagnosis due to its imaging similarities. This lesion is also characterized by a unilocular and well-defined radiolucent image with well corticated borders[1,5] as observed in immature FDs. The histopathological aspects described in immature FDs ass highly cellularized stroma showing spindle-shaped fibroblastic cells is also a feature that has been seen in central ossifying fibromas. Thus, even when lesions are similar from the imaging and histopathological perspectivies, clearly, the definitive diagnosis requires close correlation between the patient's clinical features, imaging findings and histopathology.

In conclusion, early or immature FD presents unique clinical, imaging and histopathological features when compared to mature FD. The limited number of the cases reported of immature FD so far highlights the importance of long-term follow-up of affected patients. The management of such patients should be decided on an individual basis, thus avoiding unnecessary agressive surgical procedures resulting in functional and aesthetic consequences for young patients. In addition, the immunoreactivity found for osteocalcin in osteoblasts reinforce that the process of

bone formation present in FD is independent of the stage of maturation of the lesion.

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TABLE

Table 1. Clinical and imaging features of immature FD.

Case	Age	Gender	Anatomic Site	Size of tumor	Imaging Features	Time of Evolution (months)
1	27	F	Mandible, body	4 cm	Mixed (radiopaque/radioluscent) and well delimited margins	72
2	6	F	Mandible, body	1,5 cm	Radioluscent and well delimited margins	24
3	2	M	Mandible, body	10 cm	Mixed (radiopaque/radioluscent) and well delimited margins	12
4	4	M	Maxilla and maxillary sinus	5 cm	Mixed (hypodense/ hyperdense) and well delimited margins	3
5	17	F	Mandible, angle and ramus	9 cm	Radioluscent and well delimited margins	60

FIGURES AND LEGENDS

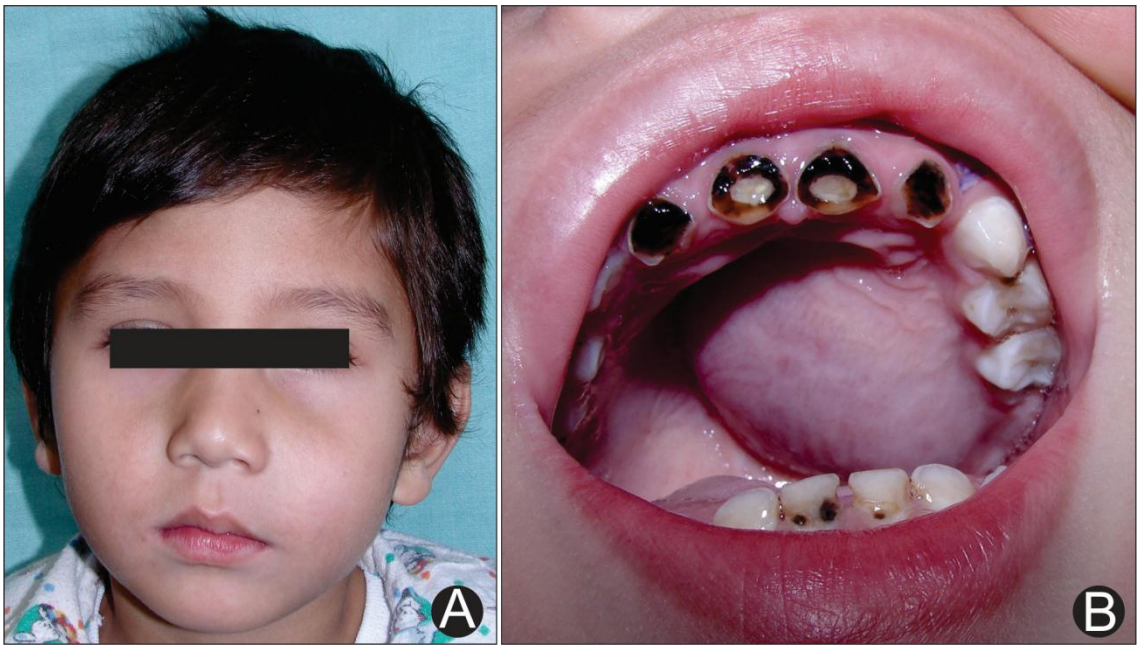

Figure 1. Clinical features of case 4. **A.** Extraoral clinical aspect showing discrete left facial asymmetry. **B.** Intraoral clinical aspect showing swelling in the left maxilla. Patient exhibiting poor dental condition.

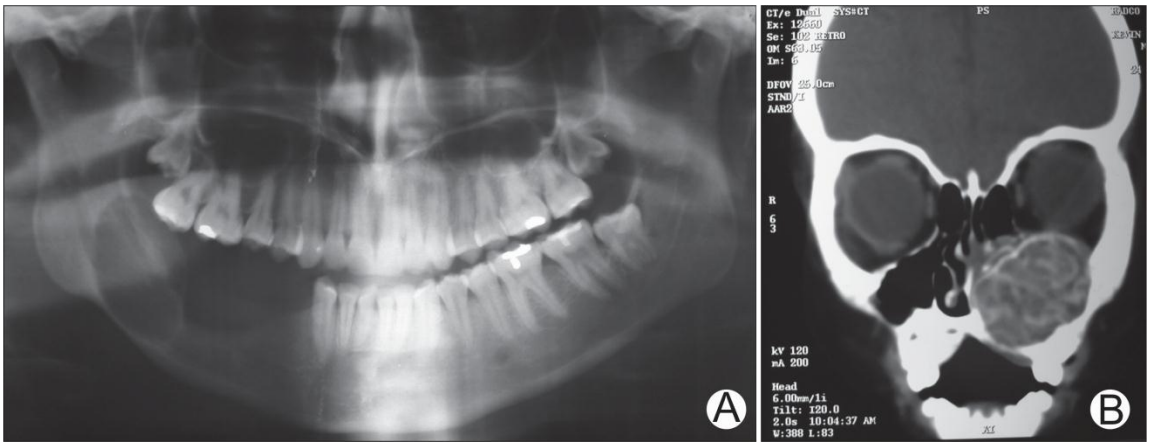

Figure 2. A. Image features case 5. Panoramic radiography showing a radioluscent and well demarcated lesion in the angle and ramus of the left mandible. **B.** Image features of case 4. Computerized tomography, coronal view. Mixed hypodense/ hyperdense image showing well delimited margins exhibiting expansion of the left maxilla and maxillary sinus.

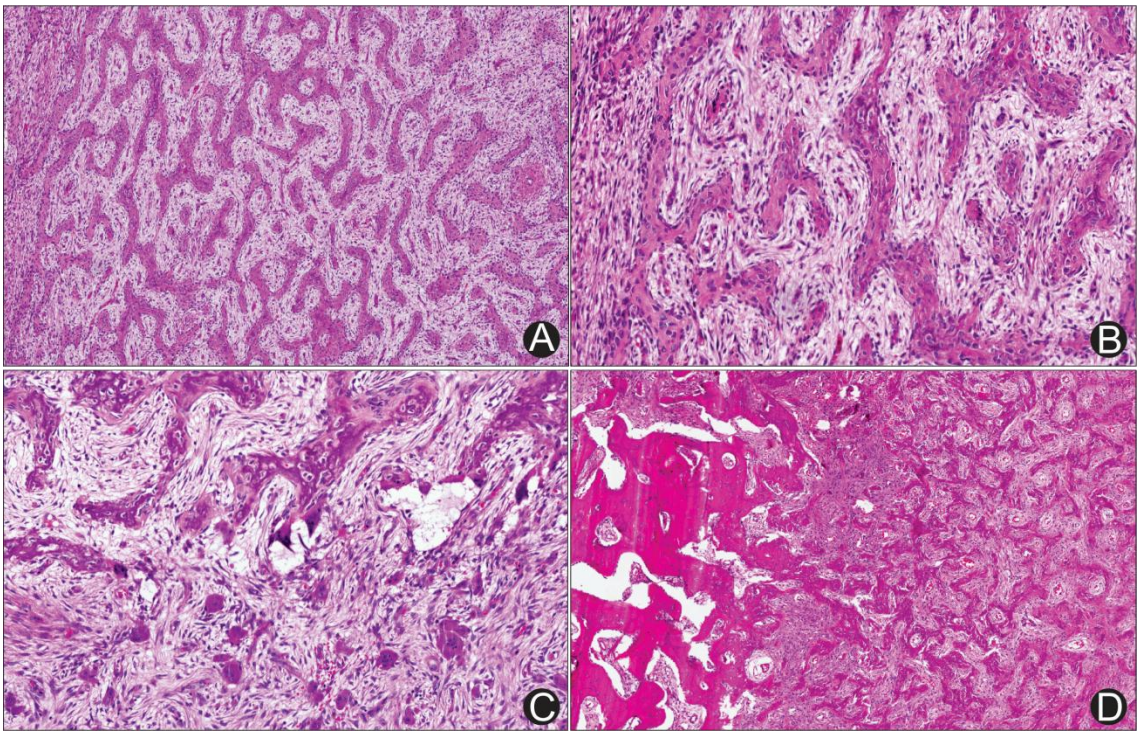

Figure 3. Histopathological features of immature fibrous dysplasia. **A.** Woven bone showing trabeculae tiny and curvilinear arranged in an hypercellular lesional stroma (HE 40X) **B.** Woven bone exhibiting osteoblast rimming (HE 100X) **C.** Large amount of multinucleated giant cell surrounding woven bone and disperse in the fibrous tissue (HE 100X). D. Cortex bone in continuity with the lesional trabecular bone (HE 40X).

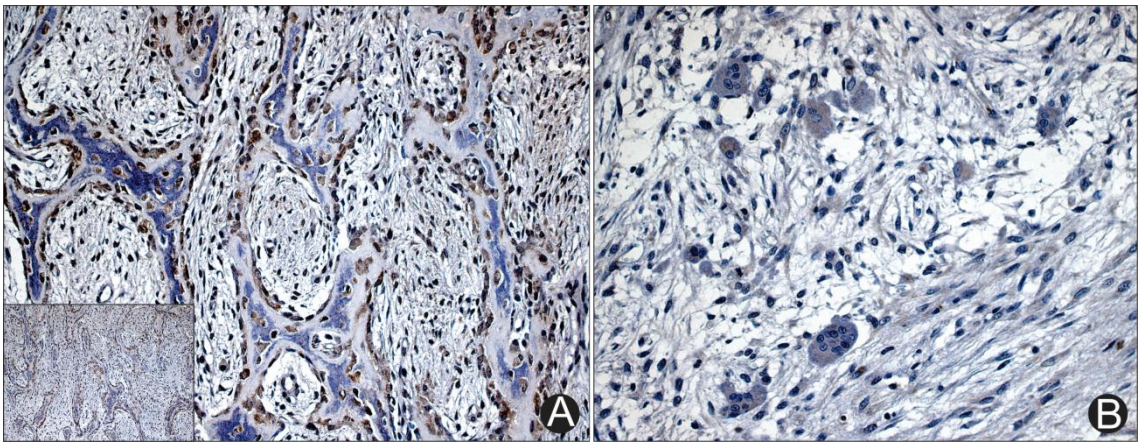

Figure 4. A. Bone surrounding osteoblasts and osteocytes showing immunoreactivity for osteocalcin (200X). **B.** Absent of immunoreactivity for osteocalcin in multinucleated giant osteoclast-like cells (200X).

CAPÍTULO 4

Artigo publicado no periódico *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology.*

Bilateral central ossifying fibroma affecting the mandible: report of an uncommon case and critical review of the literature

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Ribeiro ACP, Carlos R, Pulido-Díaz K, Gouvea AF, Vargas PA. Bilateral central ossifying fibroma affecting the mandible: report of an uncommon case and critical review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011; 111(2): e21-6. doi:10.1016/j.tripleo.2010.10.024

Bilateral central ossifying fibroma affecting the mandible: report of an uncommon case and critical review of the literature

ABSTRACT

Ossifying fibroma (OF) is a well-demarcated benign neoplasm primarily found in the jaw, composed of fibrocellular tissue and mineralized material. Occurrence of multiple OF's (synchronous) is rare in the jaws and only 10 cases have been documented. The aim of the current report is to present an additional case of bilateral central OF in the mandible empathisizing the features that distinguish this lesion to the hyperparathyroidism-jaw tumors syndrome (HPT-JT) and performing a critical review of the current literature and concepts.

Key-words: Fibro-osseous benign lesions, Ossifying fibroma, Multiple lesions, Hyperparathyroidism-jaw tumors syndrome.

INTRODUCTION

Benign fibro-osseous lesions (FOL) are a poorly defined and to some extent controversial group of lesions affecting the jaws and craniofacial bones. FOL refers to a group of pathological processes in which normal bone is replaced by fibroblasts and collagen fibers containing variable amounts of mineralized material[1-3]. This group encompasses fibrous dysplasia, benign fibro-osseous neoplasms (central ossifying fibroma), and a heterogeneous group of reactive lesions (osseous dysplasias). Because of the histopathological similarities among these lesions, the definitive diagnosis requires a precise correlation of the clinical, histopathological and the imaging findings[1,2].

The World Health Organization currently defines ossifying fibroma (OF) as a benign neoplasm which often presents well-demarcated borders and is composed histologically of fibrocellular stroma and variable amounts of mineralized material showing different morphological appearance[4]. These tumors are typically found as solitary lesions in patients lacking relevant medical history or occurrence of similar lesions in the past[5]. The occurrence of multiple or recurrent OF in the jaws is considered rare and has been associated with hormonal abnormalities such as hypercalcemia associated with hyperparathyroidism[2,5-7].

The aim of the current report is to present an unusual case of bilateral central OF affecting the mandible and to review the current knowledge regarding the occurrence of multiple ossifying fibromas in the jaws.

CASE REPORT

A 35-year-old female patient was referred for evaluation of a clinically evident facial asymmetry. The patient's chief complaint was an asymptomatic slowly progressive growth in the left mandible. Clinically, her face showed moderate asymmetry at the left mandible area (Figure 1A). Intraoral examination revealed a hard swelling in the left mandible involved by intact alveolar mucosa, while extended from the second premolar region to the retromolar area; it measured approximately 3 cm in greatest diameter (Figure 1B).

Panoramic radiograph showed a large well demarcated radiolucency, surrounded by a sclerotic border in the left body and extending into the angle of the mandible. The radiograph did not detect any evidence of calcification within the lesion. Incidentally, a contralateral well-circumscribed radiolucency with variable degrees of calcification was found, involving the region of the second and third molars (Figure 2). A computed tomography revealed an extensive unilocular and hypodense image associated with the clinical expansion of the left mandible. The other lesion located on the right mandible also showed a hypondense area with internal dense opacities mimicking snowflakes (Figure 3).

Incisional biopsies were performed in each reported lesion and both specimens showed a similar histomorpathological pattern. Hematoxylin and eosin–stained sections showed well-demarcated lesions that were separated from the surrounding bone by a thin zone of fibrous tissue. The lesions were mainly composed of cellular fibrous tissue rich in fibroblasts, with occasional areas showing a storiform pattern (Figure 4). The lesion located on the left mandible showed scarce areas of small spherical calcifications (cementum-like); in contrast, the right mandible specimen exhibited a larger amount of such calcified structures (Figure 5).

Based on the clinical, imaginological and histopathological features, a diagnosis of bilateral central OFs was rendered and dosages of serum calcium, phosphorus and parathyroid hormone (PTH) were requested in order to rule out a possible correlation between the jaw lesions and hyperparathyroidism. Serum tests showed calcium values at 9.73 mg/dL (normal range 8.4 – 11 mg/dL), phosphorus 4.2 mg/dL (normal range 2.5-5 mg/dL) and PTH 56.34 pg/mL (normal range 15-65 pg/mL). Results of blood tests (white blood cell count, red blood cell, hemoglobin and hematocrit) were all within normal limits. Thus, surgical enucleation of these lesions was performed in two different surgical interventions. During surgical removal, the lesions showed delimitation and separation from the surrounding bone, and were entirely enucleated in whole. The microscopic findings of both lesions showed identical findings to those described in the two previous incisional biopsies. The patient is still under periodic clinical and radiographic follow-up. After for 3 years, she shows no signs or evidence of recurrence and is in good health.

DISCUSSION

OF is mainly diagnosed between the 2nd and 4th decades of life, with women being affected more frequently than men[1-3]. To the best of our knowledge, multiples synchronous central OFs are rare event, with only 10 previously reported cases. The main features of these cases are summarized in Table 1.

Based on the previously published cases of multiple OFs, 7 (70%) patients were females and 3 (30%) males. The mean age is 33.8 years (ranging from 6 to 55 years old). Clinically, 5 (50%) cases presented as painless slow-growing lesions, whereas 4 (40%) cases were associated with pain. All cases were associated with facial enlargement. The present case showed similar clinical features when compared to the previously mentioned, the current patient was a 35 year-old female at the time of the diagnosis, presenting with an asymptomatic growth on her left mandibular region, causing moderate facial asymmetry.

The imaginological features were similar among the 10 cases reviewed and were characterized by well circumscribed, mainly radiolucent lesions, with intralesional calcification in 6 (60%) cases. Conservative surgery was the treatment elected in 8 (80%) patients, and in block resection was performed in 3 (30%) lesions. The mean follow-up time was 1 year (ranging from 6 to 48 months), and therefore, conclusive results regarding of the recurrence could not be reliably assessed. Recurrences were documented in 2 (20%) cases. Similarly, the present case showed radiolucent and well-circumscribed lesions with only one of them showing focal radiopacities (right side). The treatment performed in both lesions was surgical enucleation and after 3 years of follow-up no recurrence had been detected.

Multiple or recurrent OFs of the jaws had been previously reported in association with the hyperparathyroidism jaw tumor syndrome (HPT-JT). Jackson et al. (1990)[6] were the first authors to described families with multiple cases of primary hyperparathyroidism (PHPT) and jaws tumors affecting 3 generations of the same family.

HPT-JT is an inherited autosomal dominantly disorder, characterized by the occurrence of parathyroid adenomas or carcinomas, fibro-osseous lesions of the mandible and maxilla, Wilms' tumor, renal cysts, renal hamartomas, renal cortical adenomas, papillary renal cell carcinoma, pancreatic adenocarcinoma and testicular tumors[5,18]. Inactivation of the HRPT2 gene is associated with the pathogenesis of hereditary HPT-JT[2,5,7].

The association between alterations in the serum values of PTH and the presence of OFs in the jaws is highly suggestive of HPT-JT[5]. Approximately 35% of the patients presenting the syndrome have OFs while may appear as early as 13 years of age[8]. The recommended treatment in these cases is surgical removal, but there is the possibility of recurrent jaw tumors in patients with HPT-JT following surgery[7].

In the present case, serum calcium, phosphorus and PTH level values were requested to exclude a possible association with HPT-JT. It is important to highlight that among the similar cases reported, only Yih et al. (1989)[11] and Khanna and Andrade (1992)[12], mentioned that dosages of serum levels of calcium and alkaline phosphatase were requested.

The case reported by Yih et al. (1989)[11] (Table 1) have found that serum levels of alkaline phosphatase increased through the time of patient's follow-up. Interestingly, they found that the patient's mother also had an OF in the left mandible and another one in the maxilla. Unfortunately, these authors did not investigate the serum levels of PTH, which could represent a misdiagnosis of the reported case, have a family background, which is highly suggestive of HPT-JT. In the current case, the dosage of serum calcium, phosphorus and PTH levels were normal, allowing us to exclude the above mentioned association. In our opinion, this most important diagnostic criteria for patient screening was not performed, and the possibility of their relationship with HPT-JT was not adequately ruled out. In addition, in 7/10 previous reported cases[8-10,12,14,16,17], the mean of the follow-up period was not mentioned or was considered too short in order to completely rule out the possibility of the late systemic manifestation related to endocrine alterations.

The etiology and pathogenesis for both clinical forms of OFs (solitary and multiples) remain unknown. Interestingly, these different forms of OFs present very similar clinical, radiological and histophatological features, showing that they are different clinical presentations of the same pathology. Most significantly, it is important to bear in mind that in general, OFs are solitary lesions while multiple

occurrence is rare. Multiple or solitary OFs are often detected incidentally through radiographic examination of the jaws. Additionally, clinicians should be aware of the possibility of HPT-JT syndrome in young patients since this disease is usually associated with recurrent or multiples OFs of the jaws.

In conclusion, the literature concerning the clinical features and the origin of multiples OFs is very scarce and controversial. The relevance of this issue relies on the possible association of multiples OFs with HPT-JT which in turn, is associated with additional abnormalities in others organs, including malignant tumors and systemic findings.

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TABLE

Table 1. Summary of reported cases of multiple OFs of the jaws in patients not affected by the HPT-JT.

Case	Reference	Gender / Age	Site	Clinical presentation	Image features	Hormonal alterations	Treatment	Follow-up
1	Bradley and Leake, 1968	F/6	Lesion 1: right maxilla Lesion 2: right angle of the mandible	Painless, expanding mass showing marked asymmetry in the right face	RE: Multicystic lesions	NR	Right maxilla: surgical enucleation and curettage Right mandible: scheduled for removal	NR
2	Takeda and Fujioka, 1987	M/55	Lesion 1: left maxilla Lesion 2: right maxilla	Spontaneous pain and swelling of maxillary region	RE: Well circumscribed lesions showed radiolucent areas intermingled with radiopaque areas	NR	NR	Patient refused treatment

3	Hauser et al., 1989	M/35	Lesion 1: right sinus maxillary Lesion 2: left sinus maxillary	Swelling associated with bilateral proptosis, zigomatic enlargement, infraorbital nerve paresthesia, partial nasal obstruction	RE: well-circumscribed mixed radiolucent/radiopaque lesions. No evidence of root resorption was noted. CT: well- circumscribed lesion with calcified masses	NR	Right sinus maxillary: surgical enucleation Left sinus maxillary: partial hemimaxillectomy	NR
4	Yih et al., 1989	F/31	Lesion 1: left mandibular body Lesion 2: right maxilla Lesion 3: left mandible (2 years later)	Pain in the left of the face associated with the first molar	RE: well- circumscribed unilocular radiolucency	Alkaline phosphatase: 218 IU/L Serum calcium: normal limits Phosphate: normal limits	Left mandibular body and right maxilla: surgical enucleation	Residual radiolucency 2 year later No recurrence after 4 years
5	Khanna and Andrade, 1992	M/33	Lesion 1: right maxilla Lesion 2: left body of the mandible	Swelling large, hard and painless	RE: large lesions contained diffuse calcifications	Alkaline phosphatase: normal limits	Right maxilla and left body of the mandible: surgical	1 year, after the treatment the patient did

						Serum calcium: normal limits	enucleation	not return for follow -up
6	Hwang et al., 2001	F/25	Lesion 1: right mandibular body Lesion 2: left maxillary tuberosity Lesion 3: left mandibular body Lesion 4: left maxillary Lesion 5: right maxilla	Marked swelling, hard and painless, with no signs of inflammation	RE: Large calcified mass surrounded by a radiolucent halo zone with corticated margin	Blood tests were all within normal limits.	Right mandibular body: partial hemimandibulectomy Right maxilla: hemimaxillectomy	Initially the patient refused treatment – 3 years later was realized surgical remission of the lesions
7	Bertolini et al., 2002	F/37	Lesion 1: left maxilla and hard palate	Large, hard and painless slow-growing in the right and left body of the mandible and	RE: large radiolucency in the left maxilla and right body of the	NR	Right mandible: partial mandibulectomy	Mandible: No recurrence after 2 years

			Lesion 2: right body of the mandible Lesion 3: left body of the mandible	in the left maxilla	mandible. There also was a smaller lesion in the left body of the mandible. CT: revealed fibrous calcified masses that involved the left maxilla and the right and left mandibular body		Left mandible: curettage Left maxilla: intraoral surgical removal	Maxilla: No recurrence after 1 year
8	Barberi et al., 2003	F/53	Lesion 1: left infraorbital region Lesion 2: right hard palate	Slowly progressive growth without pain and/or tenderness	RE: showed partial opacification of left maxillary sinus CT scan: well-demarcated soft-tissue mass having a high density inhomogeneous for contextual several areas of low density and scattered calcifications.	NR	NR	NR

9	Stergiou et al., 2007	F/36	Lesion 1: left mandible Lesion 2: right mandible Lesion 3: left maxilla	Pain and hard swelling of mandible	RE: well- circumscribed unilocular radiolucency containing diffuse calcifications CT: well-demarcated lesions showing areas of low density and scattered calcifications	NR	Left mandible, right mandible and left maxilla: surgical enucleation and curettage	No recurrence after 6 months
10	Chindia et al., 2008	F/27	Lesion 1: right angle and body of the mandible Lesion 2: left maxilla	Painful and hard swelling of the mandible and expansion of the left maxilla	RE: Mandible lesion was corticated and maxillary lesion was less well defined with almost complete obliteration of the maxillary sinus	NR	Mandible lesion: surgical enucleation Left maxilla: surgical enucleation	Recurrence after 6 months (mandible)
11	Current case	F/35	Lesion 1: left mandible Lesion 2: right mandible	Hard swelling of the left mandible associated with moderate facial asymmetry	RE: Large radiolucency surrounded by a radiopaque halo in the left and right body of the	Serum calcium: 9.73 mg/dL Phosphorus:	Left mandible lesion: surgical enucleation Rigth mandible:	No recurrence after 3 years

					mandible CT: Unilocular and hypodense image	4.2 mg/dL PTH: 56.34 pg/mL	surgical enucleation	

NR= not reported; RE: Radiographic examination; CT: Computed tomography

FIGURES AND LEGENDS

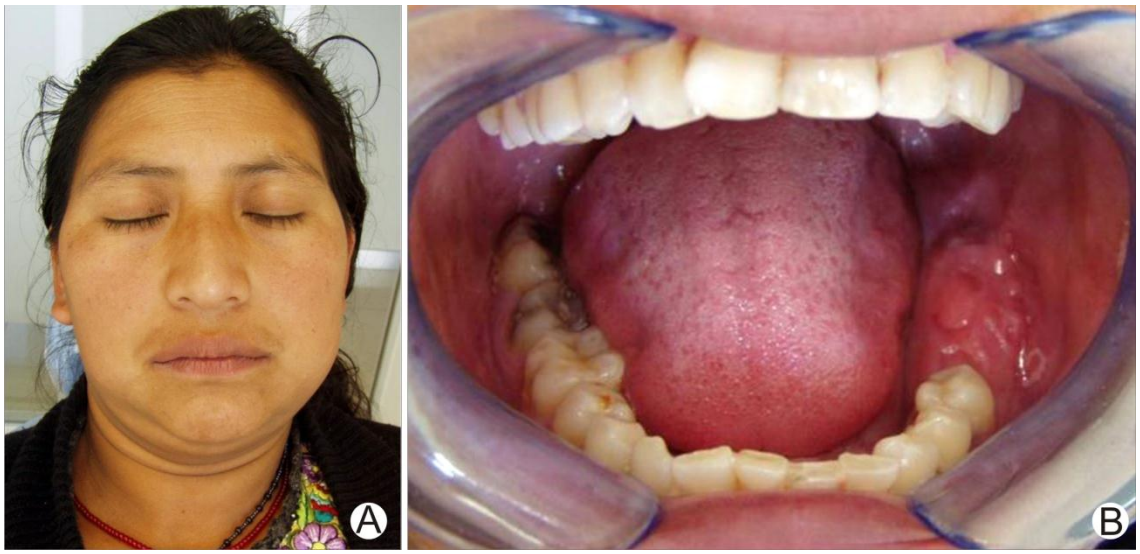

Figure 1. A. Extraoral clinical aspect showing discrete asymmetry at the left mandible. **B.** Intraoral clinical aspect showing swelling in the posterior left mandible.

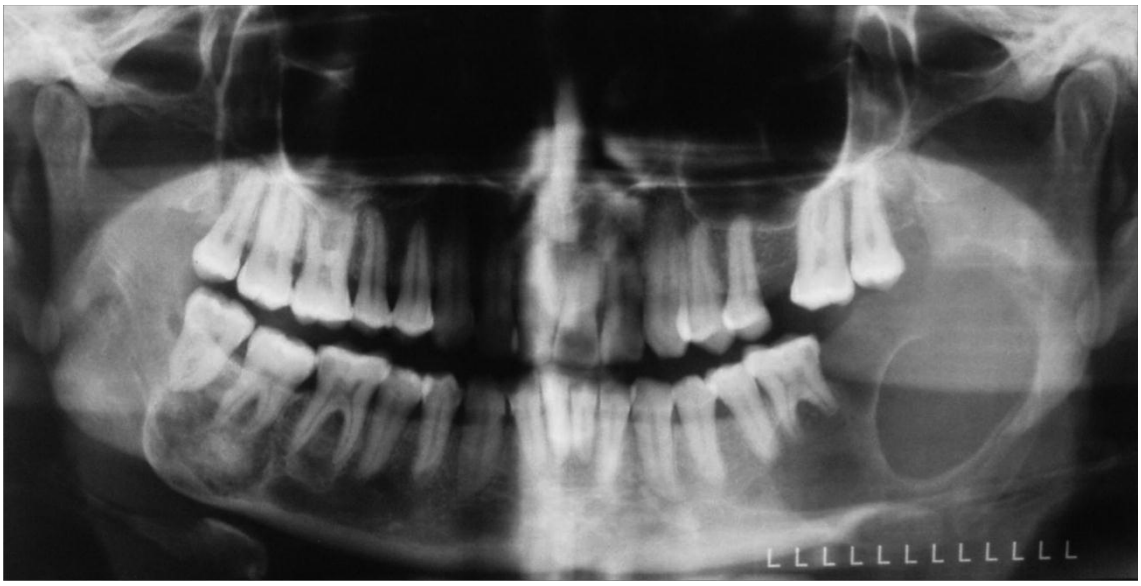

Figure 2. Radiolucid and well demarcated lesions in the left body and angle of the mandible. Mist and well circumscribed lesion in the posterior right mandible.

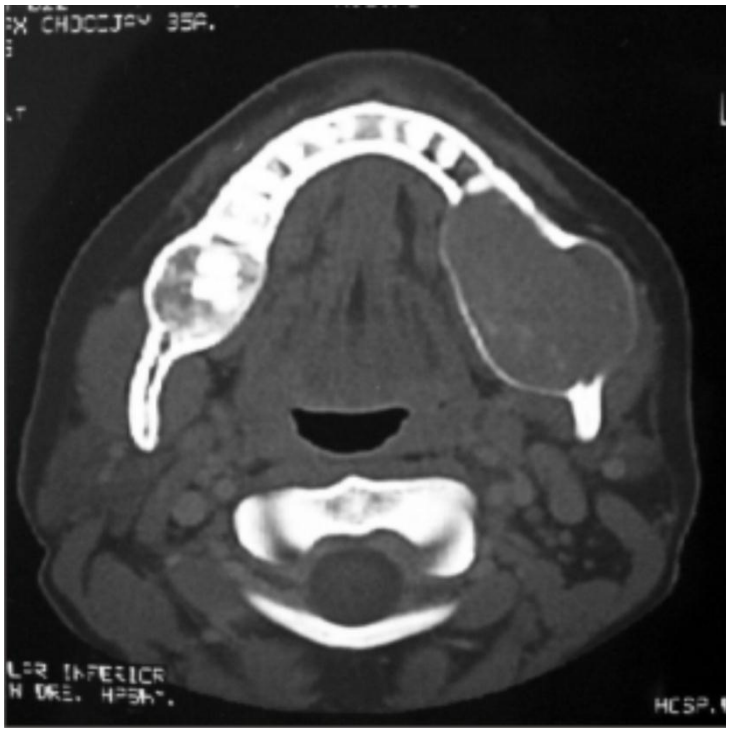

Figure 3. Hypodense and well demarcated image exhibiting expansion of the left mandible. In the right mandible a hypondense area with internal dense opacities was observed.

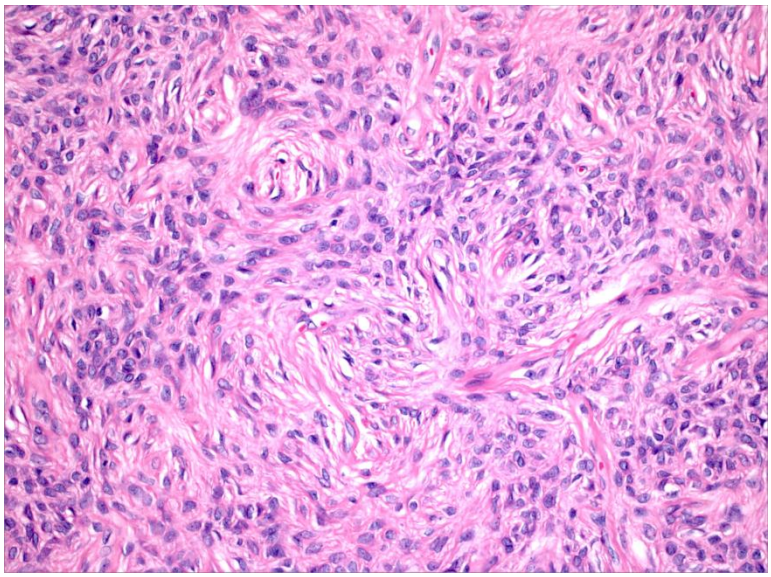

Figure 4. Storiform pattern observed in some areas of the lesion (H.E.200X).

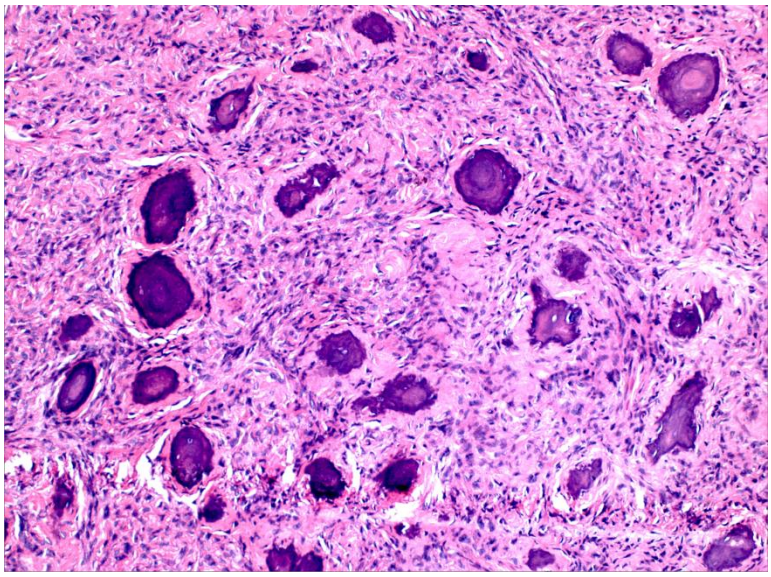

Figure 5. Cellular fibrous tissue depicturing spherical calcifications (H.E. 200X).

CAPÍTULO 5

Carta ao editor publicada no periódico *Journal of Endodontics*

Focal osseous dysplasia misdiagnosed as ossifying fibroma in a periapical region.

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Carlos R, Ribeiro ACP, Vargas PA. Focal osseous dysplasia misdiagnosed as ossifying fibroma in a periapical region. Journal of Endodontics, *In Press, Corrected Proof*, *Available online 20 May 2010.*

LETTER TO THE EDITOR

Focal osseous dysplasia misdiagnosed as ossifying fibroma in a periapical region.

Dear Editor,

The article “Ossifying fibroma misdiagnosed as chronic apical periodontitis” recently published by Ramos-Perez et al. (1) in *Journal of Endodontics* (March 2010), reports an interesting case of ossifying fibroma affecting the mandible. According to the authors, the lesion has been initially misdiagnosed as a periapical lesion. The lesion in question was radiographically described as a radiolucent, unilocular and well-circumscribed image in the periapical region of the lower right canine.

We would like make some considerations regarding the diagnosis of the current case. In our point of view, this lesion is highly suggestive of an early focal osseous dysplasia (FOD) rather than a conventional ossifying fibroma (OF). The World Health Organization (2) defined osseous dysplasias as idiopathic processes localized in the periapical region of the teeth, characterized by the replacement of normal bone by fibrous tissue and metaplastic bone.

Su et al. (3) extensively reviewed the distinguishing features between FOD and OF and observed that the curettage tissue of the FOD is often friable and presented as multiples small fragments. Conversely, OF is frequently believed to be an intact specimen. Interestingly, Ramos-Perez et al (1) reported that the lesion was composed of friable tissue which resembles the description of a FOD specimen.

Other important points that should be raised and which may reinforce our observation are the anatomical site of the lesion, the reduced dimensions of the periapical lesion (approximately 1 cm in diameter) and the lack of bone expansion. According to Su et al. (4), Speight and Carlos (5) and Eversole et al. (6), FOD was seen more frequently in the anterior region of the mandible in contrast with OF that

are more frequently diagnosed in the posterior region of the mandible. FOD are believed to have a very limited growth capacity due to its frequent well delimited features and small sizes, especially when compared with OF. Bone expansion or divergence of the involved teeth is rarely observed.

Radiographically, FOD and OF are generally found as well-circumscribed images of varying radiopacity around tooth-bearing areas (5,6). In the early stages, FODs classically present well-defined radiolucencis in the dental apices. In these cases, radiographic images may be erroneously diagnosed as an endodontic lesion (4,6). Apparently, this situation happened in the present case and lead to a probably unnecessary endodontic treatment. Therefore, we recognize how difficult the distinguishion between a FOD and a OF can be, however, it is very important to emphasize that OF is a very rare lesion, while FOD is approximately four times more frequent than OF (4) which makes the diagnosis of FOD to be much more probable than an OF in similar cases.

Finally, we feel like this case reported by Ramos-Perez et al. (1) do not reach all the clinical, radiographical and histopathological criteria for the diagnosis of OF (3,4). That said, we also believe that those similar cases reported by Sanchis et al. (7) could also have been misdiagnosed. From the best of the authors knowledge, there are no reported cases in the English-related literature that fulfil the diagnostic criteria for an OF confined to the periapical region of a single tooth that mimicked a periapical inflammatory lesion.

Most importantly, the relevance of this discussion is based on the fact that misdiagnosis in similar cases could cause overtreatment since OF and FOD have strictly different clinical behaviors and prognosis. Thus, cases of FOD, which is a very common condition, underdiagnosed as a OF could lead to wide and unnecessary bone resections with severe consequences to the patient.

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CONCLUSÕES

1. As displasias fibrosas acometem, predominantemente, pacientes do gênero feminino, na segunda e terceira década de vida, sendo a maxila o sítio de maior incidência, enquanto os fibromas ossificantes centrais são mais frequentes em pacientes do gênero feminino, na segunda e terceira década de vida, sendo a mandíbula o sítio de maior incidência.

2. A presença de fendas peri-trabeculares é uma característica histopatológica marcante das displasias fibrosas e pode ser aplicada como um novo critério diagnóstico para a diferenciação microscópica entre as displasias fibrosas e os fibromas ossificantes centrais.

3. Aparentemente, existe uma parcela das displasias fibrosas que possuem características clínicas, imaginológicas e histopatológicas peculiares quando comparadas às displasias fibrosas convencionais. Sugere-se que estas lesões sejam denominadas de “displasias fibrosas imaturas”.

4. O diagnóstico final das displasias fibrosas e dos fibromas ossificantes centrais depende, sobretudo, da correlação entre as características clínicas, imaginológicas e histopatológicas.

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* De acordo com a norma da UNICAMP/FOP, baseada na norma do International Committee of Medical Journal Editors – Grupo Vancouver. Abreviatura dos periódicos em conformidade com o Medline.

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COMITÊ DE ÉTICA EM PESQUISA
FACULDADE DE ODONTOLOGIA DE PIRACICABA
UNIVERSIDADE ESTADUAL DE CAMPINAS

CERTIFICADO

O Comitê de Ética em Pesquisa da FOP-UNICAMP certifica que o projeto de pesquisa "**Estudo clinicopatológico, imunoistoquímico, molecular e de ultraestrutura em casos de displasia fibrosa, fibroma ossificante e osteossarcoma dos ossos gnáticos**", protocolo nº **054/2008**, dos pesquisadores **ANA CAROLINA PRADO RIBEIRO, PABLO AGUSTIN VARGAS e RICARDO DELLA COLETTA**, satisfaz as exigências do Conselho Nacional de Saúde – Ministério da Saúde para as pesquisas em seres humanos e foi aprovado por este comitê em 11/06/2008.

The Ethics Committee in Research of the School of Dentistry of Piracicaba - State University of Campinas, certify that the project "**Clinicopathological, imunohistochemical, molecular and ultrastructural study of fibrous dysplasia, ossifying fibroma and osteosarcomas of the jaws**", register number **054/2008**, of **ANA CAROLINA PRADO RIBEIRO, PABLO AGUSTIN VARGAS and RICARDO DELLA COLETTA**, comply with the recommendations of the National Health Council – Ministry of Health of Brazil for research in human subjects and therefore was approved by this committee at 11/06/2008.

Prof. Pablo Agustin Vargas
Secretário
CEP/FOP/UNICAMP

Prof. Jacks Jorge Júnior
Coordenador
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