FACULDADE ILAPEO

Gabriel Haddad Kalluf

Alterações Condilares Tridimensionais em Pacientes Classe III Esquelética Submetidos à Cirurgia Ortognática – Uma Revisão Sistemática

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Tese apresentada a Faculdade ILAPEO como parte dos requisitos para obtenção de título de Doutor em Odontologia

Orientador: Prof. Dr. Augusto Ricardo Andrighetto

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Dedicatória

A minha amada esposa Daniela, companheira e inspiradora há 20 anos, e minha linda filha Marina, por preencherem minha vida de momentos maravilhosos. São minhas maiores lições de amor e perseverança! É tudo por vocês.

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Sumário

1. Artigo científico 1

De acordo com as normas do **Journal of Oral Maxillofacial Surgery,** para futura submissão.

Three-dimensional Changes in the Mandibular Condyle in Skeletal Class III Patients Treated with Orthognathic Surgery – A Systematic Review

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RESUMO

Proposição: O objetivo desta revisão sistemática foi avaliar as evidências disponíveis sobre a incidência e quantificação das alterações de superfície nos côndilos mandibulares após cirurgia ortognática por meio de osteotomia sagital bilateral da mandibula (OSBM), com ou sem cirurgia maxilar, em indivíduos simétricos ou assimétricos classe III.
Materiais e Métodos: A busca foi realizada nas bases: Pubmed, Lilacs, Web of Science, Embase, Scielo, Scopus, Ebsco, Cochrane, além do Google Acadêmico, e então registradas no International Prospective Register of Systematic Reviews (PROSPERO). Os estudos selecionados atenderam aos critérios estabelecidos pelo seguinte modelo PICO: (1) População: indivíduos com deformidades dentofaciais classe III, com idade acima de 18 anos. (2) Intervenção: cirurgia ortognática utilizando OSBM. (3) Comparação: medidas tomográficas condilares (volume, espessura, altura e largura) previamente ao procedimento cirúrgico. E (4) resultados: medidas tomográficas condilares (volume, espessura, altura e largura) no intervalo mínimo de doze meses do pós-cirúrgico.
Resultados: Inicialmente, foram identificados 800 artigos, dos quais 651 duplicatas foram excluídas, 149 foram triados e oito estudos foram selecionados para extração de dados e análise, com base nos critérios de inclusão e exclusão. Dentre os oito estudos, cinco avaliaram indivíduos classe III simétrica; e três estudos, indivíduos classe III com assimetria facial, totalizando 211 pacientes, sendo 89 do sexo masculino e 122 do sexo feminino. No total, 422 côndilos foram avaliados e, segundo os parâmetros determinados, foram observadas remodelações ósseas mínimas com médias variando entre -0,03 mm até -0,94 mm e 0,01 mm até 0,34 mm para reabsorção e aposição, respectivamente.
Conclusão: A análise dos dados obtidos constataram mínimas alterações na morfologia condilar após a cirurgia ortognática por meio de OSBM, com ou sem cirurgia maxilar, indicando maior previsibilidade na estabilidade esquelética. Os vieses observados não comprometeram a confiança nos dados analisados, os quais verificaram ausência de recidivas clínicas. Contudo, é desejável mais estudos clínicos com metodologia melhor padronizada na aquisição de imagens através de tomografia computadorizada de feixe cônico, aumentantando os níveis de confiabilidade na quantificação da remodelação e no cálculo de volume condilar.

Palavras-chave: Cirurgia ortognática; Remodelação condilar; Reabsorção condilar; Deformidade dentofacial classe III.

ABSTRACT

Purpose: The aim of this systematic review was to evaluate the available evidence on the incidence and quantification of three-dimensional changes in the mandibular condyles after orthognathic surgery by bilateral sagittal split osteotomy (BSSO), with or without maxillary surgery, in Class III symmetrical or asymmetrical individuals.
Methods: The data bases Pubmed, Lilacs, Web of Science, Embase, Scielo, Scopus, Ebsco, Cochrane, and the Google Scholar platform were surveyed and registered in the International Prospective Register of Systematic Reviews (PROSPERO). The selected studies met the criteria established by the following PICO model: (1) Population: individuals with class III dentofacial skeletal deformities and over 18 years old. (2) Intervention: orthognathic surgery using BSSO (3) Comparison: condylar tomographic measurements (volume, thickness, height and width) prior to the surgical procedure, and (4) Results: condylar tomographic measurements (volume, thickness, height and width) in the minimum interval of twelve months after surgery.
Results: Initially, 800 articles were identified, out of which 641 duplicates were excluded, 149 were screened, and eight studies were selected for data extraction and analysis, based on inclusion and exclusion criteria. Among the eight studies, five evaluated class III symmetrical individuals, while three investigated class III individuals with mandibular asymmetry. A total of 211 patients were evaluated, 89 were male and 122 were female individuals. And after investigating 422 condyles according to the determined parameters, minimal bone remodeling was observed, whose average ranged between -0.03 mm and -0.94 mm, and from 0.01 mm to 0.34 mm for resorption and apposition, respectively.
Conclusions: The data analysis revealed minimum alterations in the condylar morphology after the orthognathic surgery by BSSO, with our without maxillary surgery, indicating better predictability of the skeletal stability. The bias observed did not compromise the reliability of the data analyzed, which showed absence of clinical relapse. However, further clinical trials with standardized image acquisition methodology employing cone beam computed tomography are required to increase the reliability of the remodeling quantification and the condylar volume calculation.

Keywords: Orthognathic surgery; Condylar remodeling; Condylar resorption; Class III dentofacial deformity.

INTRODUCTION

Postoperative stability is a determining factor in the success of the orthognathic surgery since it influences the maintenance of the three-dimensional skeletal positions reached by the surgical movements[1]. Several factors might impact the postoperative instability such as the condylar displacement and lack of control of the proximal segment during the surgery, the action of muscles and soft tissues, bone fixation methods, movement amplitude, and degenerative and proliferative articular disorders[2,3]. It seems relevant to emphasize that the orthognathic surgery might result in changes in the position of articular condyles[4] Regardless of the type of mandibular osteotomy or bone fixation method used, these changes might present clinical implications for the surgical outcomes[5].

Postoperative condylar structural alterations were subdivided into two main categories, namely, physiological condylar remodeling and condylar resorption. The condylar remodeling is considered a physiological process involving the balance between resorption and bone formation, which is influenced by changes in the condylar loads and their postoperative positioning[6]. When this process goes beyond the physiological limits, bone resorption overcomes remodeling, resulting in progressive morphological alterations such as condylar mass and volume reduction, and condyle and mandibular ramus height[7].

In addition to excessive loads, there are several other suggested causes for condylar resorption such as hormonal and metabolic alterations, trauma, inflammation, anomalous growth factors, connective tissue diseases, autoimmune diseases and other pathological alterations of the temporomandibular joint in an advanced stage of degeneration[8]. The presence of post-surgical condylar resorption can lead to relapses and clinically reflect on unwanted horizontal or vertical mandibular movements. Individuals with class II dentoskeletal deformities, especially those with previously diagnosed internal joint disorders, are more likely to present condylar resorption conditions[9, 10]. However, so far, there is no consensus that post-surgical three-dimensional condylar changes in class III patients, with or without asymmetry, can alter clinical results or generate joint symptoms.

Systematic reviews have reported condylar morphological alterations following orthognatic surgery in patiens with class III dentoskeletal deformities[11,12]. However, retrospective studies published after such reviews presented data and condylar morphological evaluation criteria that allow a better understanding of risk factors and diagnosis of condylar alterations in this population. Therefore, further research is needed to better understand condylar changes after orthognathic surgery in patients with Class III dentofacial deformity.

This systematic review aimed to evaluate the existing scientific literature addressing the incidence of codylar alteration after orthognathic surgeries in class III dentoskeletal deforminties and the clinical implications of such alterations.

MATERIAL E METHODS

Protocol and registration

The systematic review protocol was planned according to the Cochrane Handbook for Systematic Review of Interventions[13]. It followed the *Preferred Reporting of Systematic Reviews and Meta-Analysis* (PRISMA)[14] list and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) on 23rd December 2022 with register number PROSPERO CRD42022383594.

The screening of titles and abstract was carried out by five researchers (ER, GHK, JMG, KT, PS, and TT) using the software SysRev.com. Disagreements were solved by consensus.

Focus question

Which alterations were observed in the condylar volume, height, thickness and width parameters in over 18-year-old patients with class III skeletal alterations in the minimum interval of twelve months after orthognathic surgery?

The focus question followed the strategy PICO(15) (Chart 1).

PICO	Detailing
Population	Individuals with class III dentoskeletal deformities and over 18 years old.
Intervention	Orthognathic surgery using bilateral sagittal split osteotomy.
Comparison	Condylar tomographic measurements (volume, thickness, height, and width) prior to the surgical procedure
Outcome	Condylar tomographic measurements (volume, thickness, height, and width) in the minimum interval of twelve months after surgery.

Chart 1 – Focus question PICO strategy

Data bases surveyed, search strategies, and selection of articles

The search was carried out in January 2023, without idiom restriction, on the following data bases: National Library of Medicine (Pubmed/Medline), Excerpta Medica Database (EMBASE), Scientific Eletronic Library Online (SCIELO), BVS (LILACS and BBO-Odontologia), Scopus, Web of Science, EBSCO, and Cochrane. The search for indexed studies and thesis occurred on the Google Scholar (grey literature). The search on the data bases employed a combination of MESH terms and synonyms related to the PICO question, along with Boolean operators (AND, OR, NOT). The software Yale Mesh Analyzer, PubReMiner, and Systematic Review Accelerator aided the term selection, keyword adaptation, and adherence to the syntactic rules of each data basis. The search final strategy for each of the data basis is detailed below (Chart 2).

Basis	**Search Key**
Pubmed	("Class III" OR "skeletal class III deformity" OR "Skeletal Class III" OR "Angle Class III" OR "Angle class III malocclusion" OR "Class III dentofacial deformity" OR "Skeletal Class III facial asymmetry" OR "Facial asymmetry" OR "Class III dentofacial deformity") AND ("Orthognathic" OR "Orthognathic Surgery" OR "Orthognathic Surgeries" OR "Orthognathic Surgery") AND (condyle OR condyles OR resorption OR resorptional OR resorptions OR resorptive OR resorptives OR "bone resorption" OR "bone Remodeling" OR "Condylar Resorption" OR "Condylar Remodeling" OR Condyles OR "Condylar hyperplasia" OR "Condylar elongation") AND (tomography)
Lilacs	("Class III" OR "skeletal class III deformity" OR "Skeletal Class III" OR "Angle Class III" OR "Angle class III malocclusion" OR "Class III dentofacial deformity" OR "Skeletal Class III facial asymmetry" OR "Facial asymmetry" OR "Class III dentofacial deformity") AND ("Orthognathic" OR "Orthognathic Surgery" OR "Orthognathic Surgeries" OR "Orthognathic Surgery") AND (condyle OR condyles OR resorption OR resorptional OR resorptions OR resorptive OR resorptives OR "bone resorption" OR "bone Remodeling" OR "Condylar Resorption" OR "Condylar Remodeling" OR Condyles OR "Condylar hyperplasia" OR "Condylar elongation") AND (tomography)
Web of Science	("skeletal class III deformity" OR "Skeletal Class III" OR "Angle Class III" OR "Angle class III malocclusion" OR "Class III dentofacial deformity" OR "Skeletal Class III facial asymmetry" OR "Facial asymmetry" OR "Class III dentofacial deformity") AND ("Orthognathic Surgery" OR "Orthognathic Surgeries" OR "Orthognathic Surgery") AND (condyle OR condyles OR resorption OR resorptional OR resorptions OR resorptive OR resorptives OR "bone resorption" OR "bone Remodeling" OR "Condylar Resorption" OR "Condylar Remodeling" OR Condyles OR "Condylar hyperplasia" OR "Condylar elongation") AND (tomography)

Embase	('skeletal class III deformity' OR 'Skeletal Class III' OR 'Angle Class III' OR 'Angle class III malocclusion' OR 'Class III dentofacial deformity' OR 'Skeletal Class III facial asymmetry' OR 'Facial asymmetry' OR 'Class III dentofacial deformity') AND ('Orthognathic Surgery' OR 'Orthognathic Surgeries' OR 'Orthognathic Surgery') AND (condyle OR condyles OR resorption OR resorptional OR resorptions OR resorptive OR resorptives OR 'bone resorption' OR 'bone Remodeling' OR 'Condylar Resorption' OR 'Condylar Remodeling' OR Condyles OR 'Condylar hyperplasia' OR 'Condylar elongation') AND (tomography)
Scielo	("skeletal class III deformity" OR "Skeletal Class III" OR "Angle Class III" OR "Angle class III malocclusion" OR "Class III dentofacial deformity" OR "Skeletal Class III facial asymmetry" OR "Facial asymmetry" OR "Class III dentofacial deformity") AND ("Orthognathic Surgery" OR "Orthognathic Surgeries" OR "Orthognathic Surgery") AND (condyle OR condyles OR resorption OR resorptional OR resorptions OR resorptive OR resorptives OR "bone resorption" OR "bone Remodeling" OR "Condylar Resorption" OR "Condylar Remodeling" OR Condyles OR "Condylar hyperplasia" OR "Condylar elongation") AND (tomography)
Scopus	("skeletal class III deformity" OR "Skeletal Class III" OR "Angle Class III" OR "Angle class III malocclusion" OR "Class III dentofacial deformity" OR "Skeletal Class III facial asymmetry" OR "Facial asymmetry" OR "Class III dentofacial deformity") AND ("Orthognathic Surgery" OR "Orthognathic Surgeries" OR "Orthognathic Surgery") AND (condyle OR condyles OR resorption OR resorptional OR resorptions OR resorptive OR resorptives OR "bone resorption" OR "bone Remodeling" OR "Condylar Resorption" OR "Condylar Remodeling" OR Condyles OR "Condylar hyperplasia" OR "Condylar elongation") AND (tomography)
Ebsco	("class III" OR "skeletal class III deformity" OR "skeletal Class III" OR "angle class III" OR "angle class III malocclusion" OR "class III dentofacial deformity" OR "skeletal class III facial asymmetry" OR "facial asymmetry" OR "Class III dentofacial deformity") AND ("orthognathic" OR "orthognathic surgery" OR "orthognathic surgeries") AND ("condyle" OR "condyles" OR "resorption" OR "resorptional" OR "resorptions" OR "resorptive" OR "resorptives" OR "bone resorption" OR "bone remodeling" OR "condylar resorption" OR "condylar remodeling" OR "condyles" OR "condylar hyperplasia" OR "condylar elongation" OR "relapse") AND ("tomography")
Cochrane	("Class III" OR "skeletal class III deformity" OR "Skeletal Class III" OR "Angle Class III" OR "Angle class III malocclusion" OR "Class III dentofacial deformity" OR "Skeletal Class III facial asymmetry" OR "Facial asymmetry" OR "Class III dentofacial deformity") AND ("Orthognathic" OR "Orthognathic Surgery" OR "Orthognathic Surgeries" OR "Orthognathic Surgery") AND (condyle OR condyles OR resorption OR resorptional OR resorptions OR resorptive OR resorptives OR "bone resorption" OR "bone Remodeling" OR "Condylar Resorption" OR "Condylar Remodeling" OR Condyles OR "Condylar hyperplasia" OR "Condylar elongation") AND (tomography)
Google Academico	(Class III OR Class III dentofacial deformity OR Facial asymmetry) AND (Orthognathic Surgery OR Orthognathic Surgeries) AND (Condylar) AND (Remodeling OR Resorption OR Remodeling OR Condyles OR Condylar hyperplasia) AND (tomography)

Chart 2 – Search strategy for each data basis

Eligibility criteria and study selection process

The eligibility criteria followed the strategy PICO[15] according to the criteria below.

Inclusion criteria: studies evaluating individuals with class II deformity, who were over 18 years old, with or without facial asymmetry, with or without open bite, and who had been submitted to bimaxillary or monomaxillary orthognathic surgery bilateral sagittal split osteotomy, whose condylar volume, height, width, and thickness parameters were determined using computed

tomography (CT) in a minimum interval of twelve months between the pre and postoperative periods. Only retrospective, prospective studies, and case series with at least 10 cases were included.

Exclusion criteria: studies investigating other types of osteotomy, maxillary surgery only, patients with previous diagnosis of temporomandibular disorders, temporomandibular joint surgery, previous facial trauma, or congenital deformities were excluded.

Next, the reviewers (ER, GHK, KT, PS, and TT) read the full articles independently and, considering the eligibility criteria, selected those potentially eligible determining their acceptance or not for data extraction (Prisma Flow 2020).

Duplicate articles were identified and eliminated using the Mendeley Reference Manager platform (Mendeley®, Elsevier, London, UK). The thorough selection of studies based on title and abstract and considering the eligibility criteria was carried out on the SysRev.com, employing balanced Article Review Priority, blinding the reviewers, and without ilimited reviews by the authors (ER, GHK, JMG, KT, PS, and TT).

Data synthesis

Data were extracted by the authors (ER, GHK, KT, PS, and TT). The primary data extracted included authors, sample size, gender, and age (mean and standard deviation). In addition, the following data were recorded: study design, presence or absence of asymmetry, surgical movement, type of osteotomy, rigid internal fixation method, and tomographic analysis method. Tables containing the results reported in relation to the height, width, thickness, and volume mean difference were registered.

Risk of bias assessments method

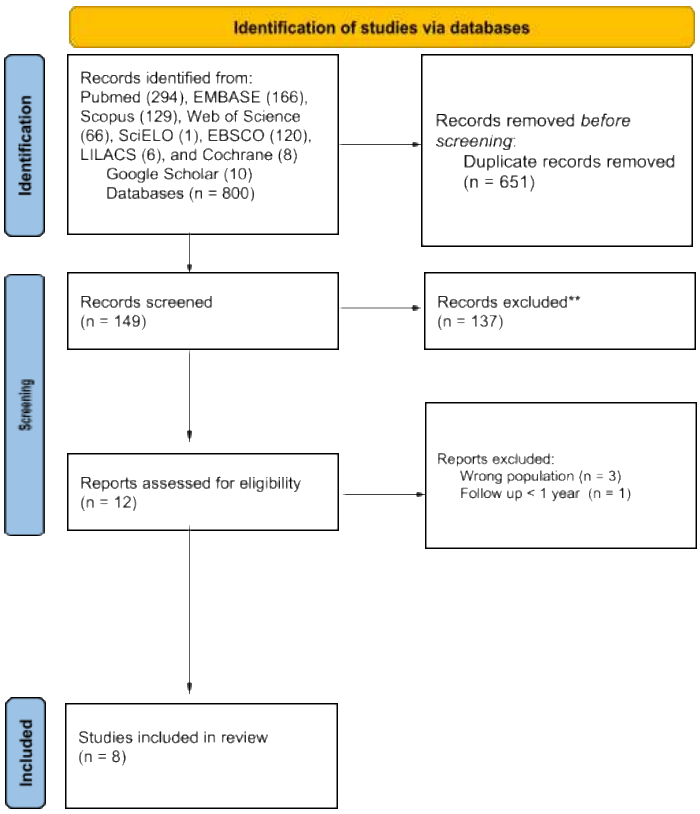
The methodological quality of the studies and disagreements were analyzed and defined by two reviewers (GHK and TT). Conflicts between examiners were solved by consensus. Bias

was classified into seven domains following the guidelines provided by ACROBAT-NRSI (A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions) developed by the Cochrane Collaboration for non-randomized studies [16]. Such bias domains include: bias due to confounding, bias in selection of participants, bias in measurement of intervention, bias due to departures from intended interventions, bias due to missing data, bias in measurement of outcome, bias in selection outcome report result. The risk of bias was classified as low, moderate, serious, or critical in each domain. Finally, based on the risk ascribed to each of the domains, the reviewers classified the total bias of the studies.

RESULTS

Selection of studies

The initial electronic search identified 800 relevant articles and after removal of duplicates 149 articles remained. Titles and abstracts were read considering the eligibility criteria and twelve articles were selected for complete reading, out of which, eight studies considered eligible for data extraction. The systematic review selection process flowchart is presented below (Chart 3)[17].



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Chart 3 – Flow chart according to the PRISMA statement

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Characteristics of the studies and demographic data

The relevant data, including the study general description, sample size, and the specificities of the groups of study, the characteristics of the populations investigated, the follow-up time for each result, and the method used for each evaluation were extracted and organized (Tables 1 and 2).

Out of the eight studies selected for data extraction and analysis, only one presented the sample size calculation[4]. The greatest study had 41 participants [18], while the smallest had 13 participants[4]. The studies reviewed evaluated 211 patients submitted to class III dentoskeletal

deformity correction, out of those, 89 were men and 122 were women and the mean age was 22.08 years (Table 1).

Author/year	Sample size	Men	Women	Mean age	Standard deviation
Takahara et al, 2022 [23]	39	18	21	23.9	5.7
Takayama et al, 2019 [24]	21	0	21	-	-
Ha et al, 2013 [20]	22	9	13	22.8	2.9
Park et al, 2012 [22]	22	11	11	20.3	3.2
Park et al, 2021[21]	23	9	14	22.5	3.7
Jha et al, 2023 [4]	13	10	3	21.2	2.6
Abotaleb at al, 2022 [19]	30	22	8	22.8	5.5
Abotaleb at al, 2022 [18]	41	10	31	21.1	2.7
Total	211	89	122	22.08	4.3

Table 1 – Demographic data

Characteristics of the studies evaluated

All studies selected were retrospective (Table 2). Only three[4,18,19] investigated patients with facial asymmetry and in one of the studies the population was only treated with mandibular setback and asymmetry correction [4]. Another study reported mandibular setback and asimmetry correction associated with maxillary advancement[18], and the third study presented mandibular setback with transversal inclination and asymmetry correction associated with maxillary advancement[19]. All studies performed bilateral sagittal split osteotomy (BSSO) in their sample, while six studies associated it with the maxillary Le Fort I osteotomy [18,19,20,21,22,23], and two studies reported mandibular surgery only[4,24]. Regarding the rigid internal fixation methods, four studies employed miniplates and monocortical screws[18,19,21,23], two studies used bicortical screws [20,22], while two studies did not inform the type of rigid internal fixation used[4,24].

The analysis of condylar alterations was carried out using computed tomography following linear measurement methods, superimposition, and volumetric comparison (Table 2).

Author / year	Experimental design	Asymmetry	Surgical movement	Osteotomy	FIR Method	Tomographic evaluation method
Takahara et al, 2022 [23]	Retrospective	no	Not reported	BSSO*** / LE FORT 1	Plate	Volumetric comparison
Takayama et al, 2019 [24]	Retrospective	no	Md setback	BSSO	Undefined FIR	Linear
Ha et al, 2013 [20]	Retrospective	no	Md setback* + Mx advancement**	BSSO / LE FORT 1	Bicortical screw	Linear
Park et al, 2012 [22]	Retrospective	no	Md setback + Mx advancement	BSSO / LE FORT 1	Bicortical screw	Linear
Park et al, 2021[21]	Retrospective	no	Md setback + Mx advancement	BSSO / LE FORT 1	Plate	Linear
Jha et al, 2023 [4]	Retrospective	yes	Md setback and asymmetry correction	BSSO	Undefined FIR	Superimposition
Abotaleb at al, 2022 [19]	Retrospective	yes	Md setback and asymmetry correction + Mx advancement	BSSO / LE FORT 1	Plate	Superimposition
Abotaleb at al, 2022 [18]	Retrospective	yes	Md setback and transversal inclination correction + Mx advancement	BSSO / LE FORT 1	Plate	Superimposition

Table 2 – Characteristics of the studies evaluated
* md – mandibular; ** mx – maxillary; *** BSSO -Bilateral sagittal split osteotomy

Risk of bias analysis

After evaluating the risk of bias, according to the Cochrane Collaboration ACROBAT-NRSI, low risk of bias was observed in 70% of the domains in the retrospective studies analyzed. The domains classified as moderate or serious refer to the population different gender and age groups, absence of blinded evaluators, lack of information about the team that carried out the intervention, and the medical institution the patients were linked to.

Studies	***Criteria***							
	Confounding	*Selection*	*Measurement*	*Follow-up*	*Missing Data*	*Outcome measurement*	*Selective Report*	*Total Risk of Bias*
Takahara et al, 2022 [23]	*Low*	*Low*	*Moderate*	*Low*	*Low*	*Moderate*	*Low*	*Moderate*
Takayama et al, 2019 [24]	*Low*	*Low*	*Moderate*	*Low*	*Low*	*Serious*	*Low*	*Serious*

Ha et al, 2013 [20]	*Low*	*Low*	*Low*	*Low*	*Low*	*Serious*	*Low*	*Serious*
Park et al, 2012 [22]	*Low*	*Low*	*Moderate*	*Low*	*Low*	*Serious*	*Low*	*Serious*
Park et al, 2021[21]	*Low*	*Low*	*Low*	*Low*	*Low*	*Serious*	*Low*	*Serious*
Jha et al, 2023 [4]	*Moderate*	*Low*	*Moderate*	*Low*	*Low*	*Moderate*	*Low*	*Moderate*
Abotaleb at al, 2022 [19]	*Moderate*	*Low*	*Moderate*	*Low*	*Low*	*Moderate*	*Low*	*Moderate*
Abotaleb at al, 2022 [18]	*Moderate*	*Low*	*Moderate*	*Low*	*Low*	*Moderate*	*Low*	*Moderate*

Table 3 – Results of the methodological quality analysis per study included using the ACROBAT-NRSI tool ("*A Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies*")[16]

Condylar parameters

The analysis of condylar height, thickness, width, and volume parameters for the studies contaning quantitative data of the 422 condyles are summarized below (Figures 1, 2, 3 and 4). Some of the studies that analyzed symmetric individuals evaluated the mean of both condyles[21,23,24] , while others presented the mean alteration of the right and left condyles separately, through linear measurements in the coronal, sagittal and axial planes[20,22]. In the studies dealing with the asymmetric population, the condyles were analyzed using tomographic superimposition and the means of the condylar alterations were calculated for both the deviated side (DS) and non-deviated side (NDS) individually[4,18,19].

Condylar height

The studies evaluated 151 individuals and 302 condyles in relation to the post-surgical condylar height (Figure 1). The bone remodeling general measurements after twelve months ranged between -0.94 and 0.18 mm. Only one study in asymmetric patients reported absence of alteration or a discrete bone apposition, which varied from 0 to 0.18 mm, in a sample of thirteen patients, which represented 6.2 % of the total sample[4]. The remaining studies showed minimum

bone resorption in both symmetric and asymmetric individuals, ranging between -0.94 and -0.1 mm[18–22,24].

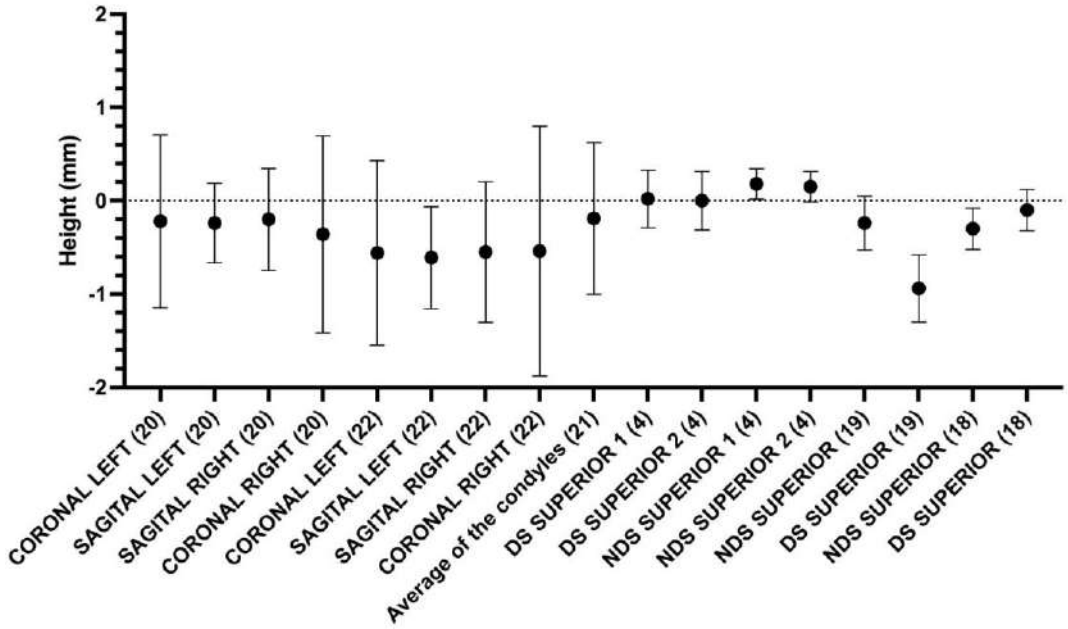


Figure 1 – Difference between the respective initial and final measurements for the height parameter. Number in parenthesis indicate the article reference. Data represented as mean and standard deviation

Condylar thickness

The evaluation of 172 individuals and 344 condyles regarding thickness was reported, and the bone remodeling mean after a period of twelve months ranged between -0.53 and 0.3 mm (Figure 2).

Out of the 176 condyles found in symmetric individuals, only 22 were unchanged after surgery[22], while 154 presented discrete resorption, ranging between -0.53 and -0.03 mm [20,21,24]. In the studies with asymmetric individuals, bone alterations were observed in the posterior and anterior poles, totaling 336 areas of tomographic interest in 169 condyles[4,18,19]. Only two studies showed evidence of bone resorption in the posterior poles of the condyles, on both the deviated side (DS) and the non-deviated side (NDS), which ranged between -0.40 and -0.04 mm[4,18,19].

The remaining 97 asymmetric condyles showed minimum bone apposition, ranging between 0.01 and 0.3 mm[4,18,19].

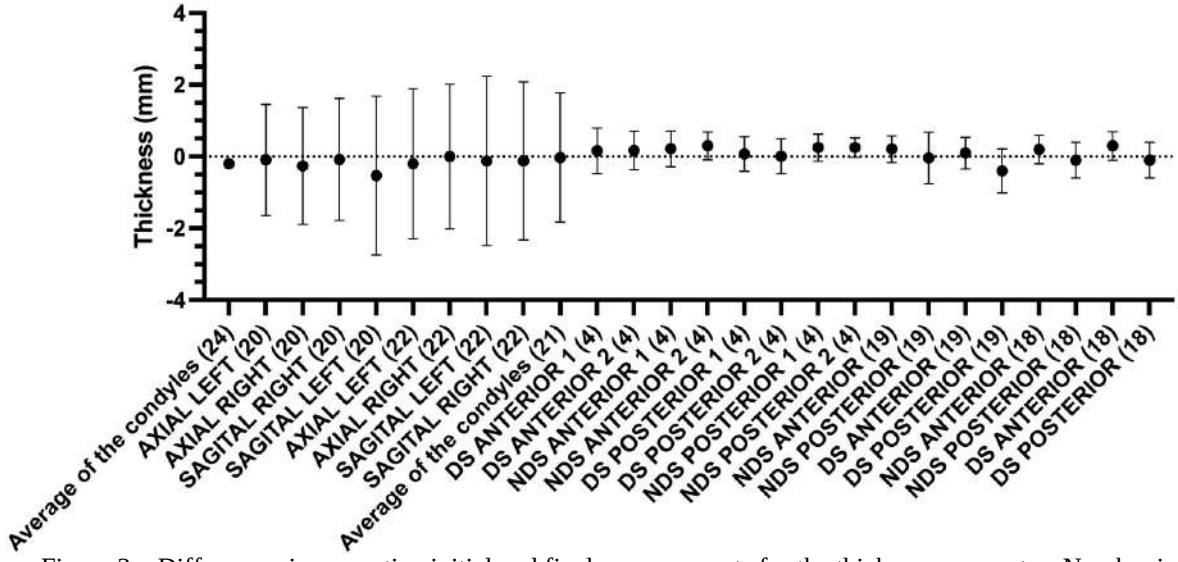


Figure 2 – Differences in respective initial and final measurements for the thickness parameter. Number in parenthesis indicate the article reference. Data presented as mean and standard deviation

Condylar width

The articles evaluated 172 individuals and 344 condyles for the condylar width, and the bone remodeling general mean (Figure 3) in the twelve-month interval ranged between -0.42 and 0.34 mm[4,18–22,24]. Among the symmetric individuals, 176 condyles were evaluated and the mean showed bone apposition in 64 condyles[22,24]. In one study[22], only the right condyles presented minimum bone apposition (0.22 mm) in the coronal linear measurement. All the remaining 112 condyles showed discrete bone resorption ranging between -0.42 and -0.03 mm. All asymmetric individuals had their condyles evaluated separately on both deviated side (DS) and non-deviated site (NDS)[4,18,19]. The remodeling on the medial and lateral poles of 168 condyles were analyzed, totaling 334 areas of tomographic interest. All studies showed unchanged widht or minimum bone apposition in the medial portion, with mean ranging between 0 and 0.34 mm. Discrete bone loss was observed only in the lateral portion of 84 condyles.

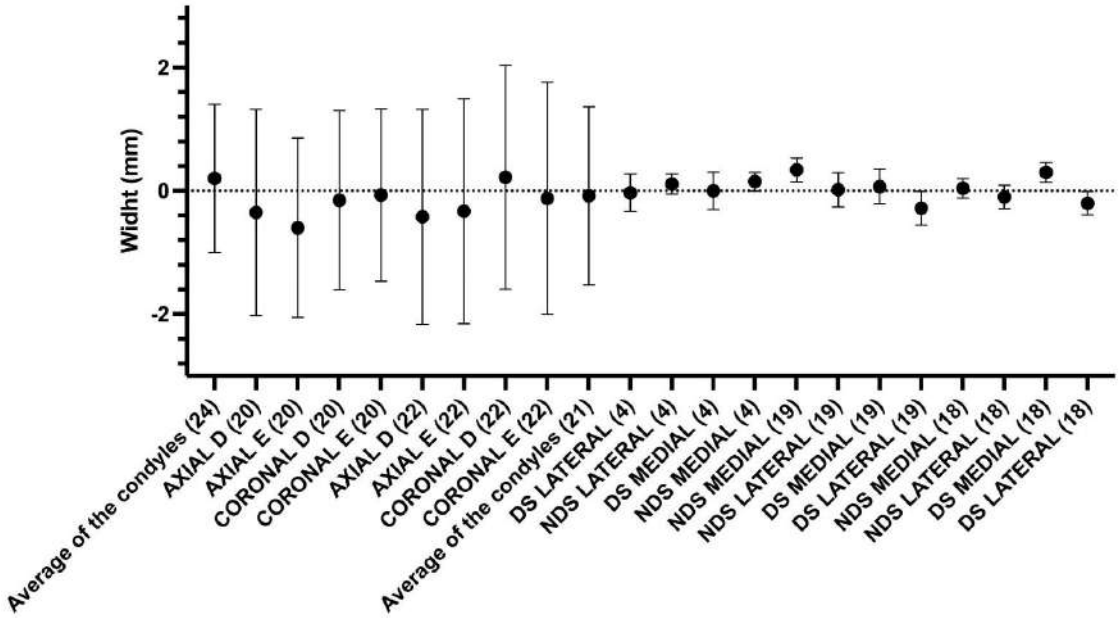


Figure 3 – Differences between the respective initial and final measurements for the width parameter. Numbers in parenthesis indicate the article reference. Data represented as mean and standard deviation

Condylar volume

The studies reported 133 individuals and 266 condyles evaluated for the post-surgical condylar volume (Figure 4). Four studies compared pre and post-surgical volumes, two of them analyzed symmetric patients and the other two evaluated asymmetric individuals[18,19,21,23]. The bone remodeling general mean after twelve months ranged between -131.65 and 8.3 mm^3. Only one study, which evaluated 82 condyles in asymmetric patients, showed increased volume, whose mean varied from 3 to 8,3 mm^3 on the non-deviated sides (NDS) and deviated sides (DS), respectively[18]. Regarding the remaningin 185 condyles, bone resorption ranging between -131.65 and -6.3 mm^3 was observed[19,21,23].

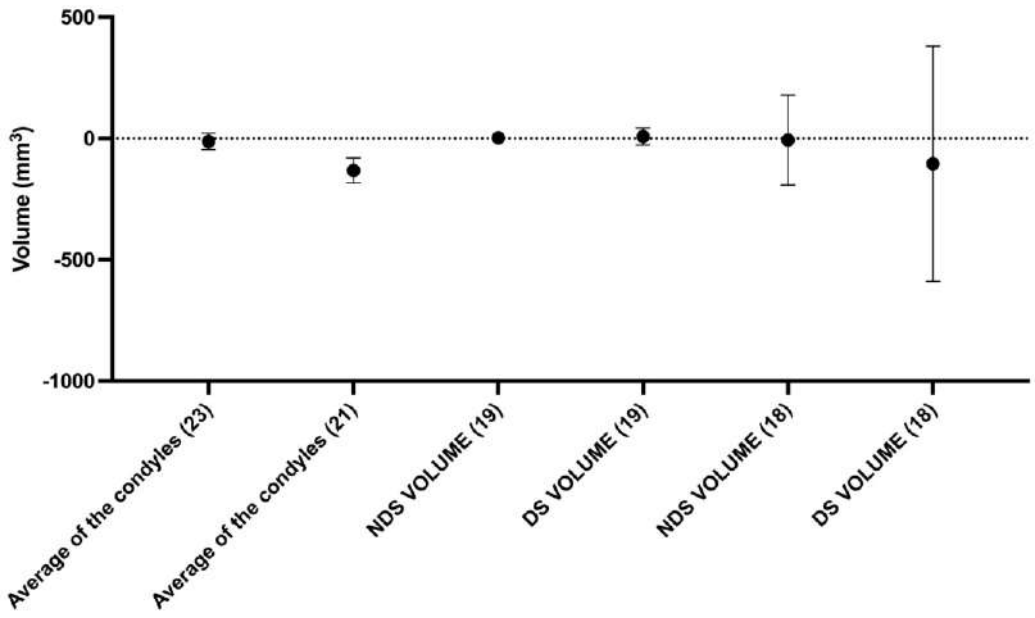


Figure 4 – Difference in the respective initial and final measurements for the volume parameter. Numbers in parenthesis indicate the article reference. Data is represented as mean and standard deviation

DISCUSSION

More severe condylar remodeling and resorptive processes have been frequently reported in cases of bimaxillary advancement in class II individuals[9]. The temporomandibular joint previous pathological and dynamic conditions might influence the development or worsen internal disorders as well as the post-surgical skeleton stability[25]. Mechanical loads on the condylar surface after orthognathic surgeries, when they are within the adaptive and physiological thresholds, should not have clinical repercussions, despite the presence of possible remodeling processes[20,22].

Inevitably, surgical movements result in a new condylar position within the mandibular fossa, which under pressure undergo some degree of remodeling[20,22]. Such condylar torque results from the new maxillomandibular position and the deflection of the mandible proximal segments after surgical movement[26]

Data from a recente systematic review investigating relapses and/or development of joint disorders in patients that underwent bimaxillary orthhognatic surgery to correct class III did not show long-term complications. However, they were not able to provide reliable

evidence due to the heterogeneity and quality of the studies included[27]. Thus, to the extent of our knowledge, there is no concrete evidence that post-surgical three-dimensional condylar alterations in class III patients, with or without asymmetry, would cause remodeling to the point of altering clinical results or generating joint signals and symptoms[11,20].

This sytematic review was conducted aiming at identifying changes on the condylar surface after orthognathic surgery in patients with class three skeletal deformity. The eight studies included evaluated 211 class III, symmetric and asymmetric individuals. All studies reported some degree of condylar remodeling, with alterations in the height, width, thickness, and volume parameters in a minimum post-surgical period of 12 months. However, these alterations neither compromised clinical results nor promoted joint symptoms[4,18–24].

From the tool used for the analysis of bias index[16], we obtained a seriou level score, mainly for the outcome domain. Some confounding bias might be ascribed to the population characteristics such as age and gender differences and the presence of asymmetries. Not all patients were operated by the same surgeon, or even assisted in the same medical center. The evaluators that took part in the intervention were not blinded. However, despite the limitations, the restrospective studies did not report sample loss, all the data proposed was reported and the results pointed out the levels of remodeling and clinical repercussion.

The mandible bilateral sagittal split osteotomy was the surgical criterion in the search for studies. Movements in the vertical, horizontal, and rotational axes are predictable and reported in a similar way when BSSO is used[28,29]. However, when analyzing condylar remodeling in class III individuals submitted to mandibular setback using two types of osteotomy, significant differences were observed in the mandible head remodeling when sagittal split ramus osteotomy (SSRO) (51.1%) and BSSO (10,3%) were used[30] .

It seems relevant to emphasize that class III skeletal deformities are not always treated surgically in the same way. Mandibular advances and counterclockwise rotations are also

carried out routinely in class III individuals, mainly in dolicofacial cases. However, great part of the sample presented here showed similar ethnic facial patterns, and the mandibular setback was the surgical movement of option for the vast majority. We believe that this improved the evluation quality of this study and is another reason why minimum alterations were found on the condylar surfaces.

Another important criterion in the selection of studies was the use of rigid internal fixation for the osteosynthesis of bone segments. This system has been widely used in orthognathic surgeries with high success rates in relation to the skeletal stability[5]. A study developed with 32 Taiwanese participants compared bone stability in mandibular setbacks via BSSO, using microplates or bicortical positional screws. Those authors suggested that both skeletal fixation methods provided good postoperative stability within a period of ten months[31]. All articles included in this review employed one or two fixation methods.

Several measurements have been discussed to quantify condylar resorption in different studies; however, this diagnosis is still controversial, depending on the association of the imaging diagnosis with the presence of clinical relapse[25]. Computed tomography was considered the technique of choice for the selection of the studies to provide greater accuracy in the detection of surface alterations than panoramic radiographs or planigraph images[32].

Despite the greater reliability of CT in the condylar morphology study, some technical obstacles must be considered. The segmentation and 3D renderization of the TMD presents difficulties due to the lower bone density in this region when compared to other areas in the mandible, in addition to its proximity to the joint disc[33]. However, most of these techniques are based on the manual design of the condylar contour in 2D cross sections from the CT, which depends on the observer and is hard to reproduce[34]. Recently, some segmentation tools using artificial intelligence have been proposed, which should provide greater accuracy and high consistency sinde the manual segmentation is time consuming and dull. An assistance

automated system might increase time efficiency, allowing the TMD routine evaluation with better cost benefit and promoting studies with more accurate results[35].

Six articles reported decreased condylar height mean[18–22,24]. Only one study, which included asymmetric patients, showed increased mean of both condyles on the deviated and non-deviated sides[4]. Reductions in the condyle superior surface are expected due to the greater possibility of local compression[20]. However, continuous bone activity, which might suggest a condylar hyperplasia condition, was not confirmed here due to the low magnitude of postoperative alterations and absence of complementary exames.

The importance of including articles with samples of asymmetric patients was based on the need to obtain a clinical prognosis supported by the condylar behavior and the skeletal and occlusal stability. Condilar hyperplasia (CH) conditions, either uni or bilateral, cause asymmetric prognathism with deviations in the mento medium line, and the volumetric differences between condyles as well as the concern with the skeletal and occlusal stability, indicate high condylectomy as the additional procedure to block the proliferative process[36].

Despite the lack of CH diagnosis in the asymmetric population, pre-surgical deviations greater than 4mm in the mento medium line were recorded. This condition might suggest growth differences between the condyles. However, in the minimum follow-up of twelve months, minimum proliferative alterations did nor present clinical repercussions[4,18,19].

Another importante piece of data that could rule out the CH condition in studies with asymmetric individuals is that no statistically significant differences were observed in the condylar remodeling mean between deviated and non-deviated sides[4,18,19].

Although this study did not correlate the post-surgical condylar position changes and the remodeling patterns, this is information of clinical impact, and some studies observed positive and significant correlation of anterior-posterior changes and alterations in the condylar height, thickness, and width[4,19,23]. However, there is no conclusive evidence that allow the

identification of the limit of the position variation needed to induce physiological remodeling or progressive condylar resorption.

Four articles compared pre and postoperative condylar volume, and minimum alterations were identified in this parameter[18,19,21,23]. One of the studies evaluated the condyles six months and six years after the procedure and found out that in the short term, a volumetric loss trend is observed. However, after six years a small gain was observed, which might characterize adaptive compensations[21].

The volumetric alterations were mainly associated with changes in the condylar height. This fact agrees with studies that state that the remodeling of this type of movement often occurs in the condyle superior and anterior superior region[20,22].

A recent study investigated the proportion between the mandibular fossa size and the condylar head in class II and III skeletal individuals and reported that the size of condyles in class II patients was significantly smaller than that in class III patients, while the mandibular fossa size was comparable in both of them. Thus, patients with mandibular prognathism show a greater condyle-fossa volume relation and are subject to smaller post-surgical positional alterations when compared with mandibular hypoplasia patients. This lower amplitude of condylar displacement might be associated with lower remodeling rates in patients with mandibular prognathism, including those with asymmetry[37].

Although there are reports that condylar resorption also occurs in class III patients, the recent literature reinforces that a good surgical prognosis with healthy temporomandibular joints. The clinical relapse that might suggest a pathological condylar resorption condition was not identified in the articles surveyed, indicating safety of this type of procedure. Although some data have shown significant differences in the bone remodeling levels between deviated and non-deviated condyles in asymmetric patients, these size alterations were not able to cause clinical relapse. Future studies might include condylar morphology analysis in hyperdivergent

class III patients, submitted to bimaxillary advancement and occlusal plane counterclockwise rotations.

CONCLUSION

The analysis of the data obtained indicated minimum alteration in the condylar morphology, at least up to twelve months after orthognathic surgery via BSSO, with or without maxillary surgery in class III symmetric or asymmetric individuals, indicating predictability regarding skeletal stability.

The bias observed by the ACROBAT NRSI tool did not compromisse the reliability of the data analyzed, which revealed absence of relapse in patients. However, more clinical trials are required with a better standardized methodology for the acquisition of tomographic images and quantification of the condylar remodeling.

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2. Artigo científico 2

De acordo com as normas do **Journal of Oral Maxillofacial Surgery,** para futura submissão.

Odontogenic Myxoma in Adolescents - Report of Two Cases

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RESUMO

O mixoma odontogênico (MO) é um tumor benigno, de origem mesenquimal, comportamento localmente agressivo e crescimento lento. É uma lesão rara, não encapsulada, e suas características imagenológicas são semelhantes a de outros tumores que acometem a maxila e mandíbula. Clinicamente, podem ser assintomáticos, em casos mais severos, podem acometer estruturas dentárias e nervosas. O diagnóstico é feito com base nos exames imagenológicos e histopatológicos. Não há diretrizes claras para o tratamento cirúrgico, sendo recomendados vários tipos de abordagens, embasadas no tamanho e localização do tumor. Os tratamentos recomendados visam minimizar recorrências e vão desde ressecções cirúrgicas, com margem de segurança, até curetagens associadas a métodos alternativos como a crioterapia. Não há um prognóstico generalizado para estas lesões e cada caso deve ser avaliado individualmente. O presente trabalho tem como objetivo discutir fatores importantes que devem ser considerados na determinação da abordagem cirúrgica, e relatar dois casos clínicos em pacientes adolescentes, um deles tratado por ressecção com auxilio de guia de ostectomia produzido virtualmente, e outro por curetagem seguida de crioterapia, com acompanhamento de quatro e cinco anos, respectivamente, sem evidências de recidiva.

Palavras-chave: Mixoma odontogênico; Crioterapia; Tumores odontogênicos.

ABSTRACT

Odontogenic myxoma (OM) is a benign tumor of mesenchymal origin, locally aggressive behavior, and slow growth. It is a rare, unencapsulated lesion and its imaging characteristics are similar to those of other disorders that affect the maxilla and mandible. Clinically it can be asymptomatic, and in more severe cases it can affect dental and nervous structures. The diagnosis is based on imaging and histopathological examinations. There are no guidelines for surgical treatment, and several types of approaches are recommended, based on the size and location of the tumor. Recommended treatments aim to minimize recurrences and range from surgical resections, with a safety margin, to curettage associated with alternative methods such as cryotherapy. There is no generalized prognosis for this type of injury and each case must be evaluated individually. This paper aims to discuss important factors that should be considered in guiding the therapeutic approach, and to report two clinical cases in adolescent patients. One of the patients was treated by resection aided by a virtually produced osteotomy guide, while the other underwent curettage with cryotherapy. They had a 4 and 5-year follow up, respectively and showed no evidence of recurrence.

Keywords: Odontogenic myxoma; Cryotherapy; Odontogenic tumors.

INTRODUCTION

Odontogenic myxoma (OM) is a rare benign tumor, representing from 3 to 5% of odontogenic tumors and can lead to high relapse rates after treatment. It has an ectomesenchymal origin and is not encapsulated. This tumor usually affects the mandibular bone of young adults, with no gender predilection[1]. It constitutes a heterogeneous group with different histopathological characteristics and several clinical manifestations, which, despite being considered benign, is locally aggressive, slow-growing, and can reach considerable size[2]. In addition to cortical bone expansion, it can cause tooth displacement and occlusion changes, but root resorption is rarely observed[3,4].

Regarding clinical examination, these tumors produce few symptoms, presenting a firm expansive mass in the maxillomandibular complex, with or without displacement and/or mobility of the associated teeth[5]. More developed lesions might present signs and symptoms such as swelling caused by bone expansion, pain, paresthesia, and damage to dental elements close to it or contained in the lesion[6]. Odontogenic myxomas more frequently affect the mandible body and angle regions as well as the ascending ramus. When the zygomatic bone and the maxillary sinus are affected, a more severe condition is observed due to their destruction power[7].

Their imaging characteristics include unilocular or multilocular radiolucent lesions[8], and several terms have been used to describe these characteristics such as “soap bubble” and “honeycomb” aspect. However, none was considered specific of these lesions due to the variety of images produced and similarity between its differential diagnoses[9]. Due to their clinical and imaging similarity with other maxillary lesions, it is necessary to resort to the differential diagnosis to prevent the use of an unsuitable treatment. According to the imaging aspects, the OM differential diagnosis includes the following lesions: ameloblastoma, aneurysmal bone cyst, intraosseous hemangioma, cherubism, giant cell lesion, keratocyst, and osteosarcoma[10, 11].

Their histological features include fusiform, round, angular cells embedded in abounding mucoid stroma or randomly arranged in a loose myxoid containing only some collagen fibrils, in the presence or absence of odontogenic epithelium islands[12]. Many theories support the OM odontogenic origin due to the histological similarity between the lesions and the pulp ectomesenchyma, constant association with missing or not erupted teeth and occasional presence of inactive odontogenic epithelium, as well as its unusual occurrence in other parts of the body[13]. Small lesions are usually treated with curettage provided that a thorough follow up of at least 5 years is kept[11]. However, larger lesions require complete removal with a safety margin, segmental resections or hemi-mandibulectomy followed by bone reconstruction[14, 15].

In general, the prognosis is favorable; however, relapse might occur. The mean frequency of recurrence is 25%, depending on the treatment, and it usually occurs within two years after the surgical intervention[16]. However, this tumor does not present malignant potential[4].

Conservative treatments might include enucleation, curettage, and marginal resection. Cryotherapy is a technique applied as an ancillary in conservative treatments. Its principle is based on tissue destruction by freezing, which is called cryolesion. Decreased tissue temperature results in the formation of ice crystals in the extracellular medium, which increases the electrolyte concentration. This creates a hyperosmotic environment that results in water osmosis outside the cells generating increased concentration of intracellular electrolytes, pH alteration, and protein denaturation. After defrosting, a new cooling provokes the formation of ice crystals in the intracellular medium. When the ice melts, the extracellular medium becomes slightly more hypotonic, water goes inside the cells, the cell volume increases and the cell membrane breaks[17,18].

A basic cryotherapy protocol to be used in maxillary neoplastic lesions is based on repetitive cycles of freezing, slow defrosting, and maintenance of the frozen tissue for a period

of 5 to 10 minutes, directly in the affected area, to help the removal of neoplasia or abnormal cell elements, without the need for extending the surgical margin[18]. Liquid nitrogen is the most common and efficient option when cryotherapy is chosen for the treatment. In such case, immediate and long-term consequences of cryotherapy must be taken into consideration when choosing the treatment whenever important anatomic structures such as the airways are close to the area to be treated using this method[17].

Exacerbated local inflammatory reaction caused by cryotherapy might provoke severe edema within the hours following the procedure. In addition, hemorrhage during the surgery, immediately after the local defrosting process is a strong possibility. Also, although cryosurgery causes necrosis of the host bone cells, it keeps the inorganic bone structure, which, despite acting as the substrate for the formation of a new tissue, might result in mandible weakness and risk of pathological fracture[19].

This study aimed to present two clinical cases of odontogenic myxoma in adolescent patients. One of the patients was treated using en bloc resection aided by virtual planning and osteotomy guide, while the other was treated in a conservative way by applying curettage and marginal bone debriding followed by liquid nitrogen cryotherapy.

CASE REPORT

Case 1

A 14-year-old female patient was referred by another professional with a panoramic radiography showing osteolytic signals on the left mandible ramus. She presented absence of intra or extra oral signals or any other clinical symptom. The tomographic image revealed broad radiolucent lesion involving the left mandible ascending ramus, which was well delimited and with a multilocular aspect and septated by straight bony trabeculae (Figure 1 A , B and C).

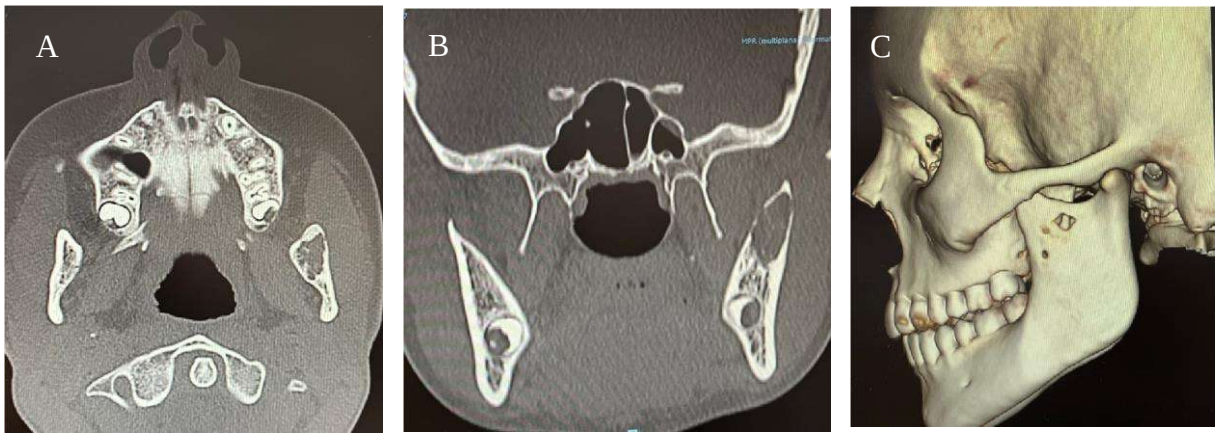

Figure 1 – Preoperative computed tomography evidencing osteolytic lesion of the mandible ascending ramus; (A) Axial cross section, (B) Coronal cross section and (C) 3D reconstruction

Curettage with incisional biopsy was carried out with access through the lesion vestibular face. The tissue presented a light non-gelatinous soft substance all over the exposed area (Figure 2). The report histopathological examination revealed conjunctive tissue with myxoid areas related to increased cell areas containing fusocellular elements (Appendix 1).

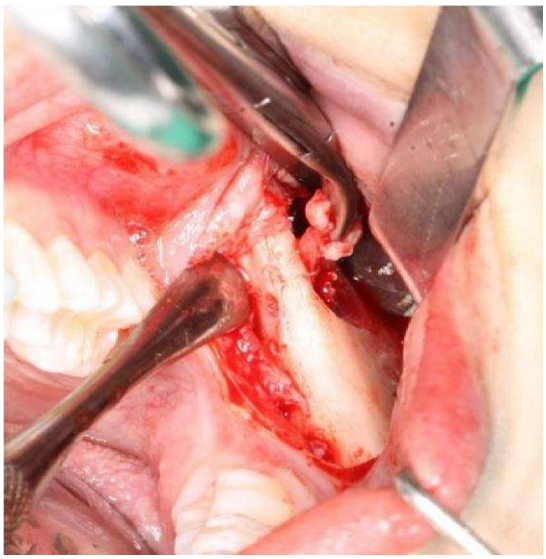

Figure 2 - Incisional biopsy

The tomographic reconstruction studies determined the lesion limits and the virtual planning for the construction of an osteotomy surgical guide that could guarantee an exeresis with suitable safety margins. By associating CAD-CAM and 3D tomographic imaging, a surgical guide was prepared in a filament printer along with the mandible biomodel, and the

perfect adjustment of the parts was confirmed (Figure 3 A and B). The lesion extension allowed a design with preservation of structures such as the mandible foramen, lower alveolar nerve, and mandible condyle.

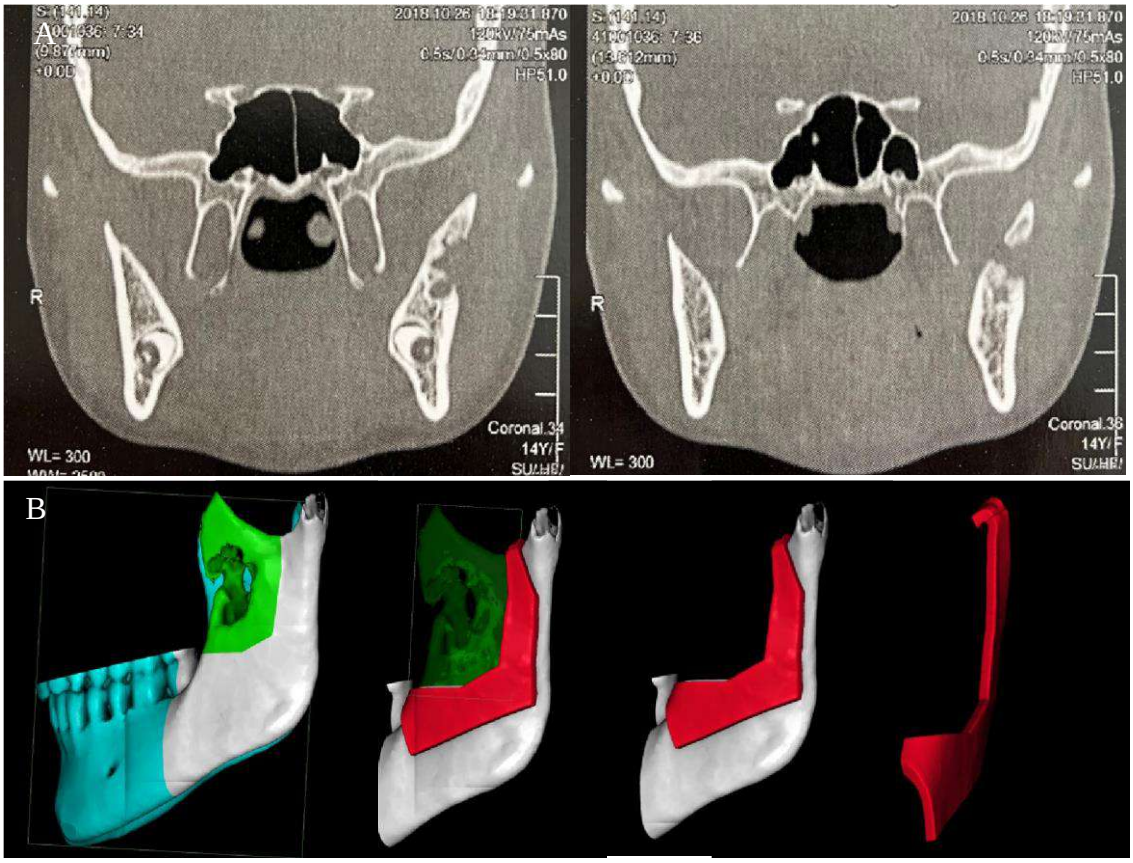

Figure 3 – (A) Lesion tomographic images six months after the biopsy. (B) Virtually produced osteotomy guide based on the lesion limits and safety margin

The surgical procedure was carried out under general anesthesia and nasotracheal intubation. The intraoral access was via vestibular incision to the left mandible ascending ramus, which allowed the visualization of the whole ramus and coronoid process. After adapting the incision guide supported by the mandibular notch, the en bloc resection was performed aided by the piezoelectric motor and complemented with multilayered cutters up to the limit of the surgical guide (Figure 4 A and B).

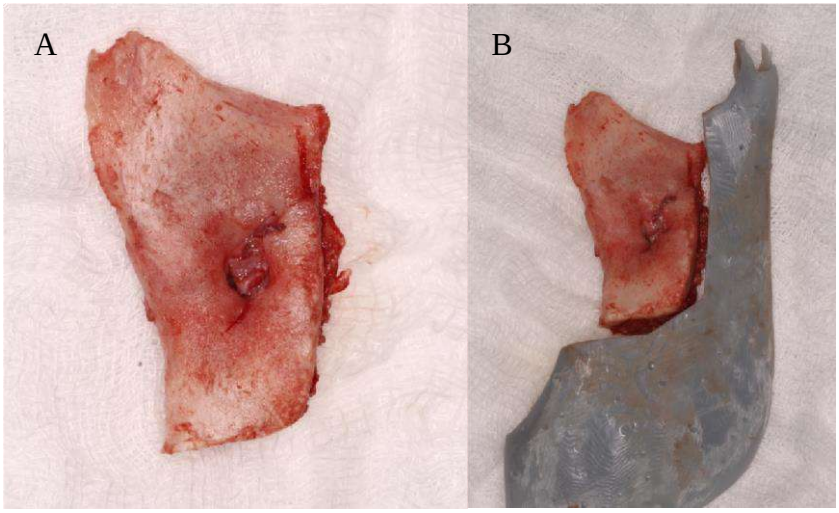

Figure 4 – (A) Coronary portion of the resected mandible. (B) Virtually produced osteotomy guide based on the lesion limits and the safety margin

The the histopathological examination of the surgical sample definitely confirmed the odontogenic myxoma diagnosis by the proliferation of fusiform cells in a star-like arrangement in myxoid stroma (Figure 5 A, B and Appendix 2).

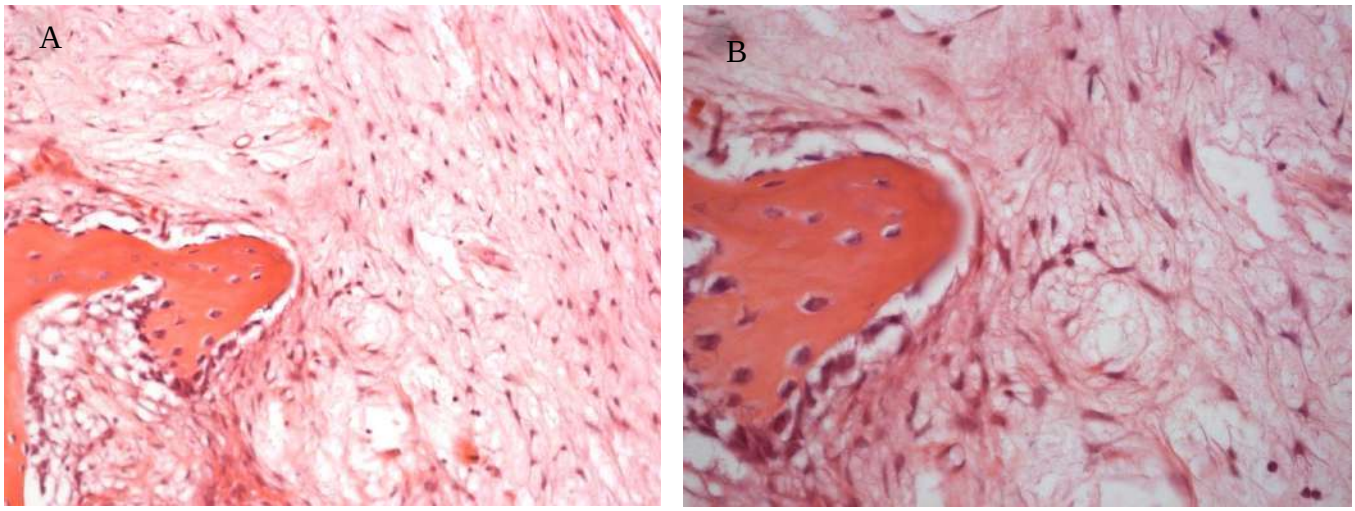

Figure 5 – Optical microscopy histological cross section (20x and 40x) confirmed the odontogenic myxoma diagnosis

In a four-year postoperative follow-up, good mouth opening and preserved mandibular movements were observed as well as absence of neuropraxic lesion or facial asymmetry. The

tomographic examination presented a surgical area with normal bone neoformation and without evidence of lesion recurrence (Figure 6).

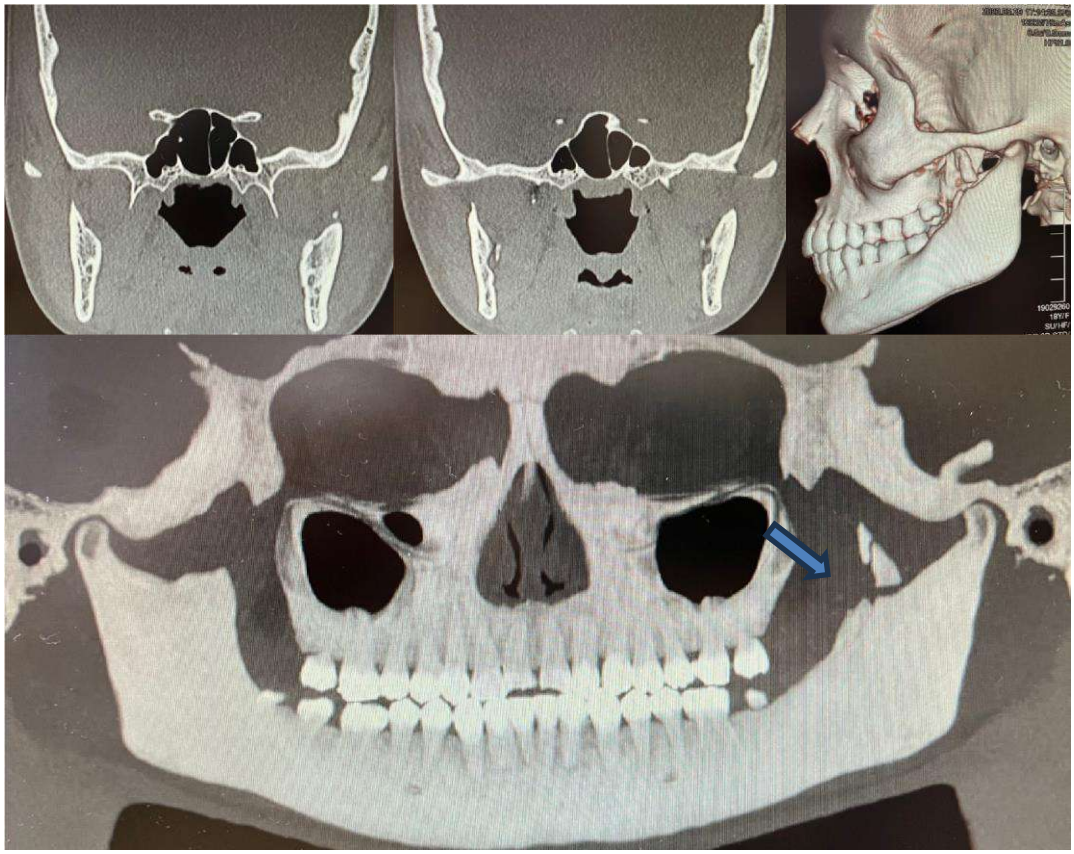

Figure 6 – Postoperative tomographic aspect after four years, showing normal bone repair with supposed formation of a new coronoid process indicated by the blue arrow

Case 2

A 13-year-old male patient assisted by the cleft lip and palate referral service appeared in a routine appointment presenting a panoramic radiography where a radiolucent image was observed in the right mandibular body basal region, with teeth 47 and 48 involved in the lesion, which extended to the mandibular ramus (Figure 7A). In the clinical examination, he did not present any apparent symptom or signal. He was submitted to the tomographic examination, which confirmed a well-circumscribed osteolytic area, with well-defined limits and resorption of the surrounding cortical bone (Figure 7B).

The incisional biopsy was carried out through the vestibular access in the mandible angle and body, along with the simultaneous 48 extraction. The microscopic analysis revealed neoplastic areas of predominantly mesenchymal origin, composed by myxoid conjunctive tissue, with a mucoid matrix and areas of fibrous aspect. These characteristics associated with the tomographic examination allowed the conclusion of an odontogenic myxoma diagnosis (Figure 8 A, B and Appendix 3).

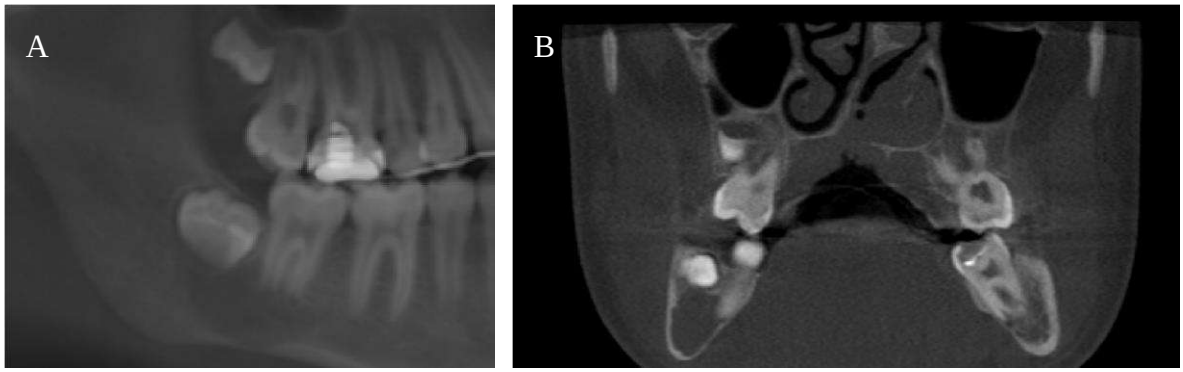

Figure 7 – (A) Initial radiographic and (B) tomographic aspect showing a translucent central lesion on the right basal region

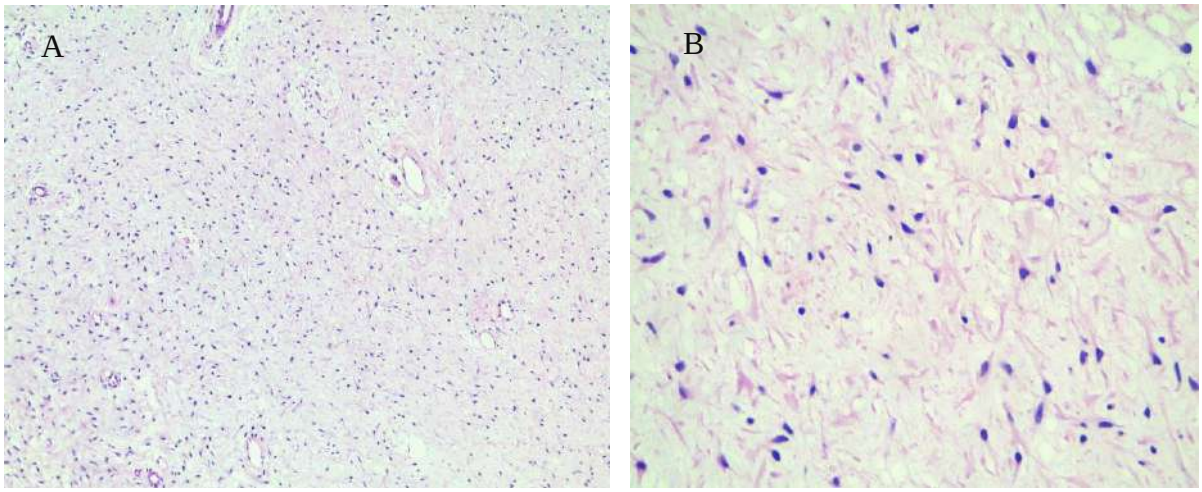

Figure 8 – Optical microscopy histological (10x and 40x) cross section confirmed the odontogenic myxoma diagnosis

After obtaining the diagnosis, the curettage of the lesion associated with peripheral osteotomy and followed by liquid nitrogen cryotherapy was planned. When the patient was prepared (serum exams and pre-anesthetic evaluation) the surgical procedure was carried out

in hospital, under general anesthesia and nasotracheal intubation. The intraoral access included intra-sulcular incision vestibular to teeth 44, 45, 46, and 47, associated with an oblique anterior incision, vestibular to tooth 44. We decided to extract tooth 47, due to its involvement in the lesion, and a surgical window was created by using multiblade burs to access the lesion and allow the curettage. The material obtained from the curettage, remaining bone fragments, and tooth 47 were all sent to the histopathological microscopic examination. After the curettage, a peripheral osteotomy was performed using large diameter multiblade spherical burs for debriding the lesion margins and eliminate tumor remnants (Figure 9 A and B). Dry gauze was interposed between the exposed bone tissue and the oral mucosa and around the whole tumor area aiming to protect the adjacent structures that would not be frozen. Next, the cryotherapy treatment started with liquid nitrogen spray in the tumor cavity. The applications on the cavity walls were carried out in three times of one minute in continuous spray with 5-minute intervals between each application, covering all the walls of the cavity and repeating the same protocol up to the conclusion of the applications (Figure 10 A and B).

After the end of the suture and removal of the oropharyngeal cover, the patient presented profuse bleeding in the operated region. The suture was removed, and the flap reopened to identify the bleeding origin. We observed that the hemorrhage originated in the lesion basal region and the floor of the mouth, close to the mylohyoid muscle. To control the bleeding and prevent future episodes, the areas were cauterized. The region was sutured again, and no bleeding was identified in the immediate and late postoperative period.

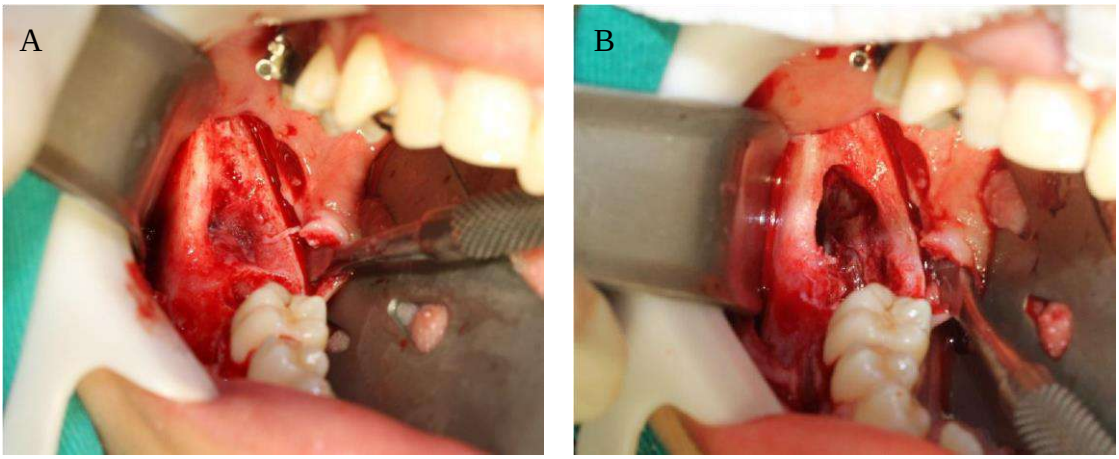

Figure 9 – (A) Flap exposing the edge crest, and (B) curettage followed by peripheral osteotomy

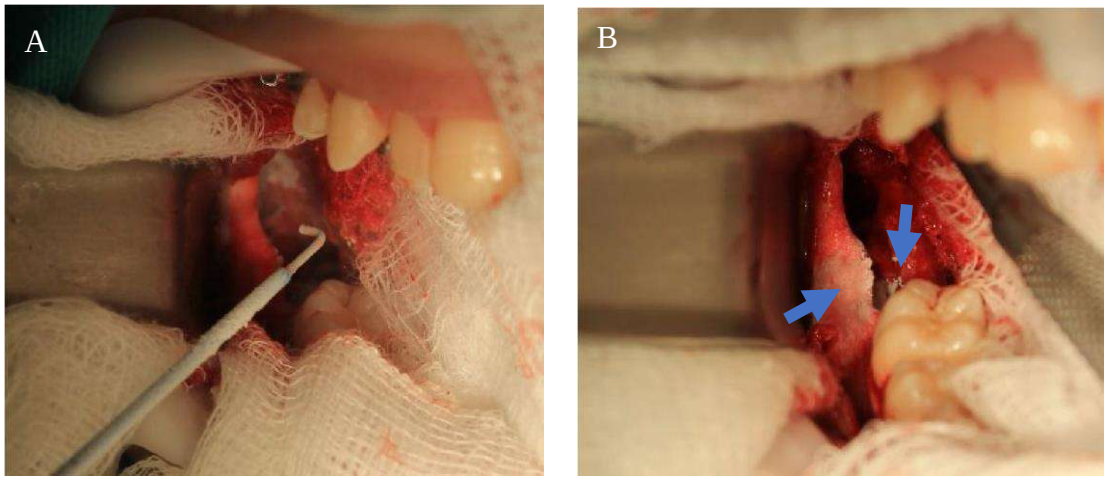

Figure 10 – (A) liquid nitrogen applications on the cavity walls, and (B) frozen bone crystals indicated by blue arrows

We decided to keep the patient in nasotracheal intubation, sedated and under surveillance at the intensive care unit (ICU) due to the risk of exacerbated edema and obstruction of airways. The patient presented a relevant edema condition on the right submandibular region before the end of the 24-hour postoperative period, which confirmed the correct conduct of keeping the airways via nasotracheal intubation and ICU assistance. The patient was treated with antibiotic medication of empirical choice, 500 mg tranexamic acid at each 12 hours, 500mg hydrocortisone soon after the procedure, which was kept with a 100mg dose at each 6 horas during the first 24 postoperative hours and ice pack applied to the right submandibular region at each 20 minutes for 48 hours, which was substituted with hot pack

applied after that period. Such procedures allowed extubation on the third day after surgery and hospital discharge on the fourth day, with peripheral action painkiller prescription, if needed. The histological analysis confirmed the diagnosis of fibromyxoma (Figure 11 A, B and Appendix 4)

Tomographic follow-up at six and twelve months after surgery were carried out in the first year, and after that period, once a year for five years, and no signs of relapse were observed (Figure 12 A and B).

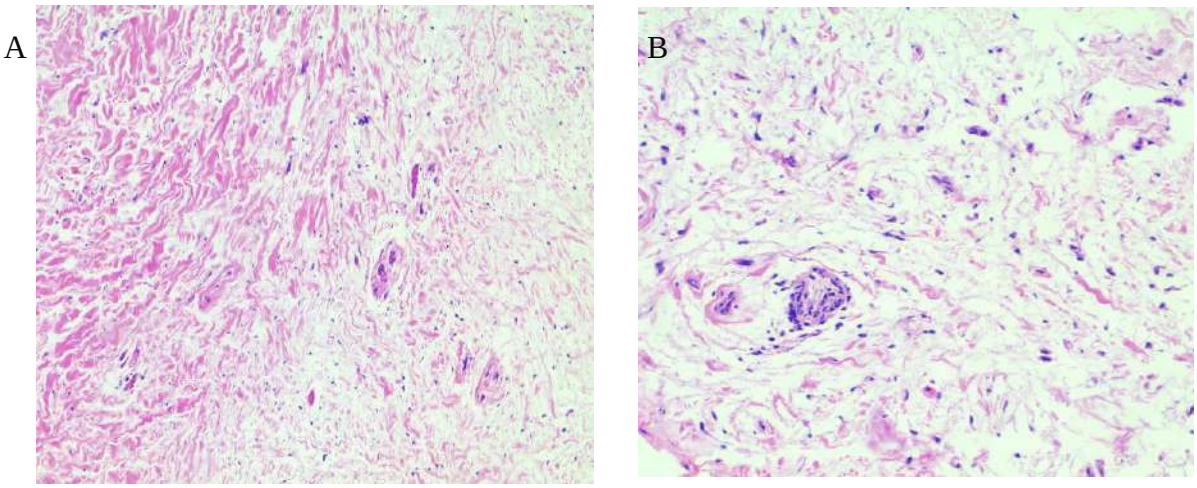

Figure 11 – Optical microscopy histological cross section (10x and 20x) confirmed the diagnosis od odontogenic fibromyxoma

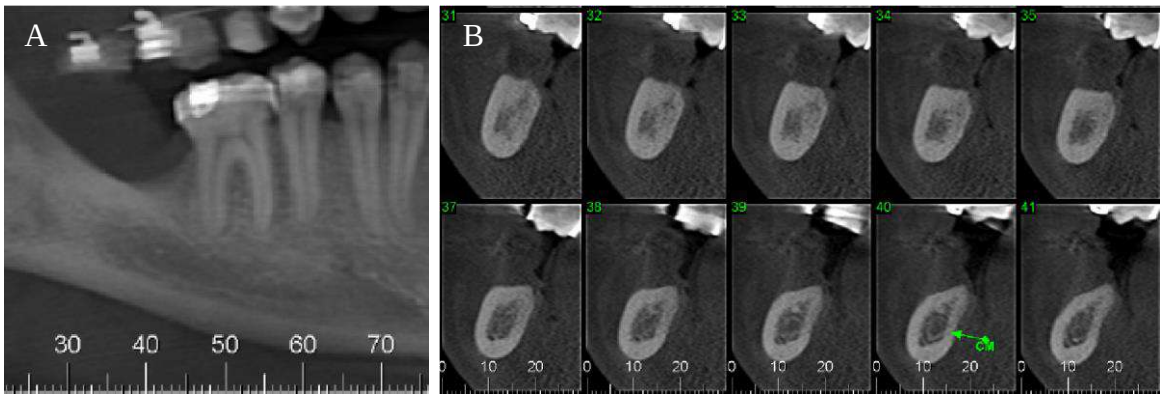

Figure 12 – Tomographic evaluation after five years showing normal bone formation, no sign of relapse. (A) Panoramic cross section, and (B) Coronal cross sections of the affected area

DISCUSSION

The odontogenic myxoma is a rare tumor and its diagnosis process demands effort in the search of clinical and imaging details. Its slow growth might lead to late diagnosis when it is already spread and has invaded adjacent anatomical structures[20]. The myxoma treatment is unavoidably surgical, with several protocols already described in the literature and the technique of choice depends on its size and proximity of adjacent dental and neural structures[8].

In the first case reported, the guided surgery allowed the definition of a safety margin and the exact replication of the conduct planned, preserving neural structures and the mandibular condyle. The good evolution of that case is due to the lesion location, which although presenting moderate size, kept those structures out of the safety margin. In the 4-year follow-up, tomographic examinations showed a tumor free healing and bone growth in the resection foreground, which suggests new formation of the mandible coronoid process.

Each case reported was diagnosed in individuals of different gender and adolescents. However, some authors have stated that OM shows no gender predilection[21], some studies have reported higher incidence in female and young patients[22,23].

In a review of 6,000 bone tumors in the Mayo Clinic, all myxoma cases reported were mandibular with a few cases affecting non-toothed areas[24]. The first case reported was diagnosed in an unusual location involving the mandibular ramus and part of the coronoid, without involving toothed areas, which associated with the early diagnosis allowed resection with further damage.

Bone reconstructions using preoperative virtual models were already described for mandibular reconstruction[24, 25, 26]. Although the real time navigated surgical procedure can be used instead of printed biomodels, those software programs are complex and biomedical engineers must be involved[24]. It seems relevant to emphasize that the evolution of

stereolithographic models has improved the surgical predictability from the recreation of defect. And the production of resection guides[27].

Although the safety margin definition depends on the operator analysis during the virtual planning, the expectation is to achieve a quite accurate surgical procedure in relation to the design. In the case reported, the fact that it was a procedure carried out via intraoral access in a region of difficult visualization and surgical access, the use of a guide was an important help in the osteotomy reproduction.

The ideal management of benign lesions that present aggressive biological behavior that might relapse would be the one that provided, in addition to the full lesion exeresis the least functional and esthetic impairment. Thus, cryosurgery outstands among the maxillofacial surgery[28]. Although the surgical intervention is the treatment of choice for odontogenic myxomas, some issues have been raised in relation to the type of treatment to be used in each case. It seems relevant to emphasize that once the postoperative control is duly performed, an early diagnosed recurrent lesion does not imply in treatment failure and can be removed with a relatively simple procedure, without having to undergo major surgical interventions with difficult recovery[29].

We observed that the curettage with peripheral osteotomy of the lesion associated with the cryotherapy action mechanism as an ancillary procedure played a fundamental role in the relapse prevention in a five-year period. One of the cryotherapy choice criteria was the fact that it was not a relapsed tumor, in which case the resection with safety margin would be indicated[8]. However, some studies have reported that even in local relapse conditions without complications, repeating the cryosurgical approach might present viable outcomes, in addition to avoiding major bone defects and functional impairment[28].

Due to the approach in the mandibular body and angle region followed by a hemorrhagic condition, we opted for keeping the patient intubated, sedated and observed, since we predicted

exacerbated edema of retromandibular and submandibular spaces due to the cryotherapy. This procedure prevented postoperative complications resulting from the impairment of airways.

The low temperatures applied reduce the bone repair capacity[30], which can extent up to 1 cm deep depending on the freezing method and local conditions[31]. Clinical studies already reported this situation from the fifth weeks after surgery onwards up to the twenty-fourth week, with an approximate mean of twelve weeks, which confirms experimental studies in which the cooled mandible showed severe weakening around the eighth week, mainly in lesions whose diameter was over 4 cm, becoming susceptible to pathological fracture episodes[32, 18]. Considering the characteristics of the bone defect caused in the case reported, the patient was instructed to keep a soft diet for fourteen weeks due to the inevitable frailty.

The application protocols used in the cryotherapy in maxillomandibular bone lesions range between 10 seconds and 8 minutes[28]. The former was the shortest time analyzed in a study using rabbits[33]. However, several authors, in cases reports and literature reviews, follow basic principles of cryotherapy as an ancillary treatment of maxillomandibular bone lesions, by applying at least 2 cycles with spontaneous reheating intervals of at least 5 minutes[28,34,35]. In the second case reported in this study, the application of liquid nitrogen spray in three cycles of one minute each with a five-minute interval between them for reheating was performed. The procedure included all the walls of the cavity of a lesion diagnosed as odontogenic myxoma in mandibular body. The 5-year follow-up showed that the treatment was successful, without fractures, good healing evolution and no evidence of lesion relapse.

However, the absence of a defined therapeutic protocol allied to the lack of scientific method, since most of the studies are descriptions of the authors' clinical and surgical experiences, should encourage standardized research to securely state the effectiveness of the treatment.

FINAL CONSIDERATIONS

The printed surgical guide, designed based on 3D virtual simulation, allowed a procedure with relatively short surgical time and easy resection via intraoral access, thus, justifying a more conservative surgical approach in the treatment of odontogenic myxoma of the mandible ramus. However, for the treatment of the same lesion in mandible body, the surgery associating curettage and debriding with liquid nitrogen spray cryotherapy applied with safety procedures allowed a quite conservative treatment, without bone resection and minimum consequences, resulting in the absence of radiologic signals of relapse for 5 years.

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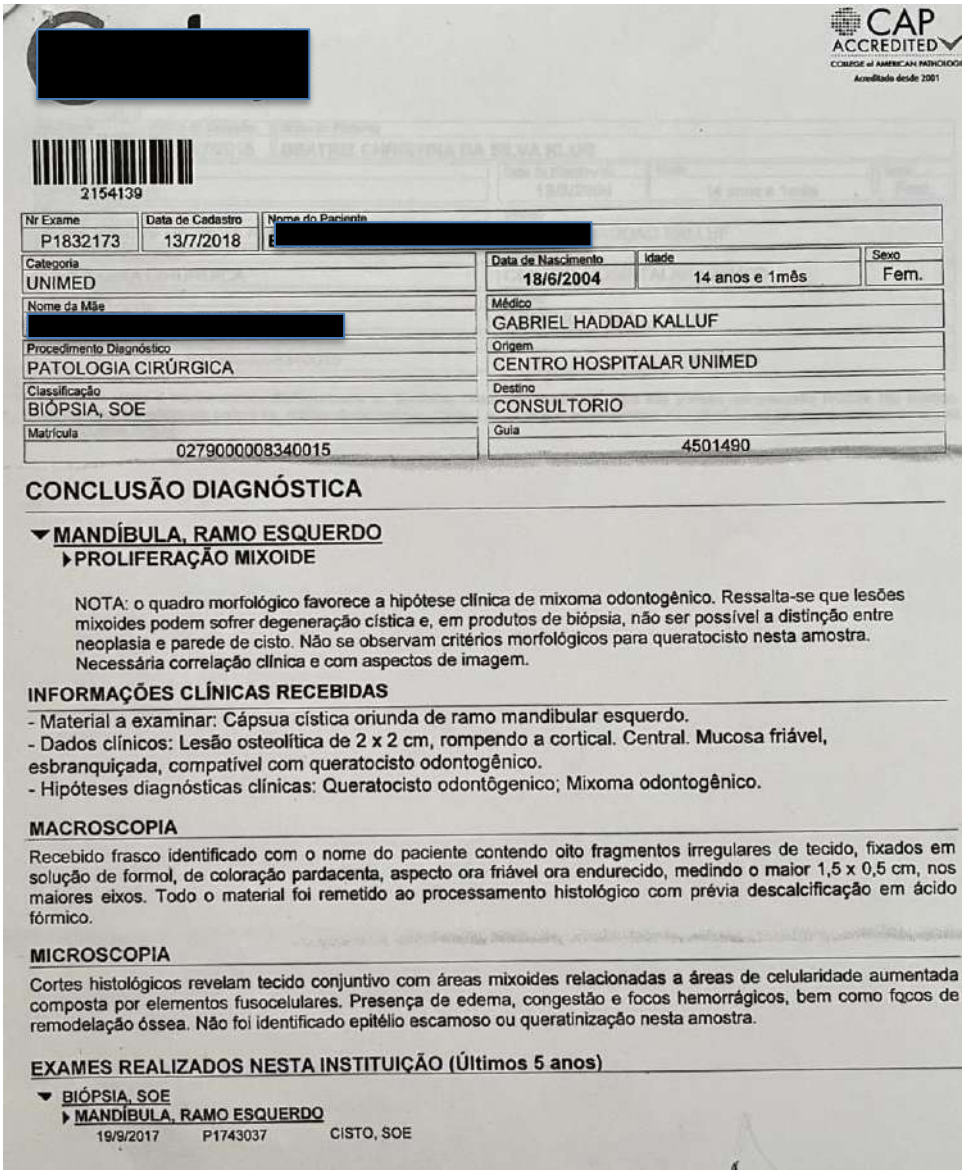
APPENDIX 1

Incisional biopsy report. Case 1



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Nr Exame	Data de Cadastro	Nome do Paciente
P1832173	13/7/2018	[redacted]

Categoria	Data de Nascimento	Idade	Sexo
UNIMED	18/6/2004	14 anos e 1mês	Fem.

Nome da Mãe	Médico
[redacted]	GABRIEL HADDAD KALLUF

Procedimento Diagnóstico	Origem
PATOLOGIA CIRÚRGICA	CENTRO HOSPITALAR UNIMED

Classificação	Destino
BIÓPSIA, SOE	CONSULTORIO

Matrícula	Guia
027900000834001 5	4501490

CONCLUSÃO DIAGNÓSTICA

MANDÍBULA, RAMO ESQUERDO
PROLIFERAÇÃO MIXOIDE

NOTA: o quadro morfológico favorece a hipótese clínica de mixoma odontogênico. Ressalta-se que lesões mixoides podem sofrer degeneração cística e, em produtos de biópsia, não ser possível a distinção entre neoplasia e parede de cisto. Não se observam critérios morfológicos para queratocisto nesta amostra. Necessária correlação clínica e com aspectos de imagem.

INFORMAÇÕES CLÍNICAS RECEBIDAS

- Material a examinar: Cápsua cística oriunda de ramo mandibular esquerdo.
- Dados clínicos: Lesão osteolítica de 2 x 2 cm, rompendo a cortical. Central. Mucosa friável, esbranquiçada, compatível com queratocisto odontogênico.
- Hipóteses diagnósticas clínicas: Queratocisto odontôgenico; Mixoma odontogênico.

MACROSCOPIA

Recebido frasco identificado com o nome do paciente contendo oito fragmentos irregulares de tecido, fixados em solução de formol, de coloração pardacenta, aspecto ora friável ora endurecido, medindo o maior 1,5 x 0,5 cm, nos maiores eixos. Todo o material foi remetido ao processamento histológico com prévia descalcificação em ácido fórmico.

MICROSCOPIA

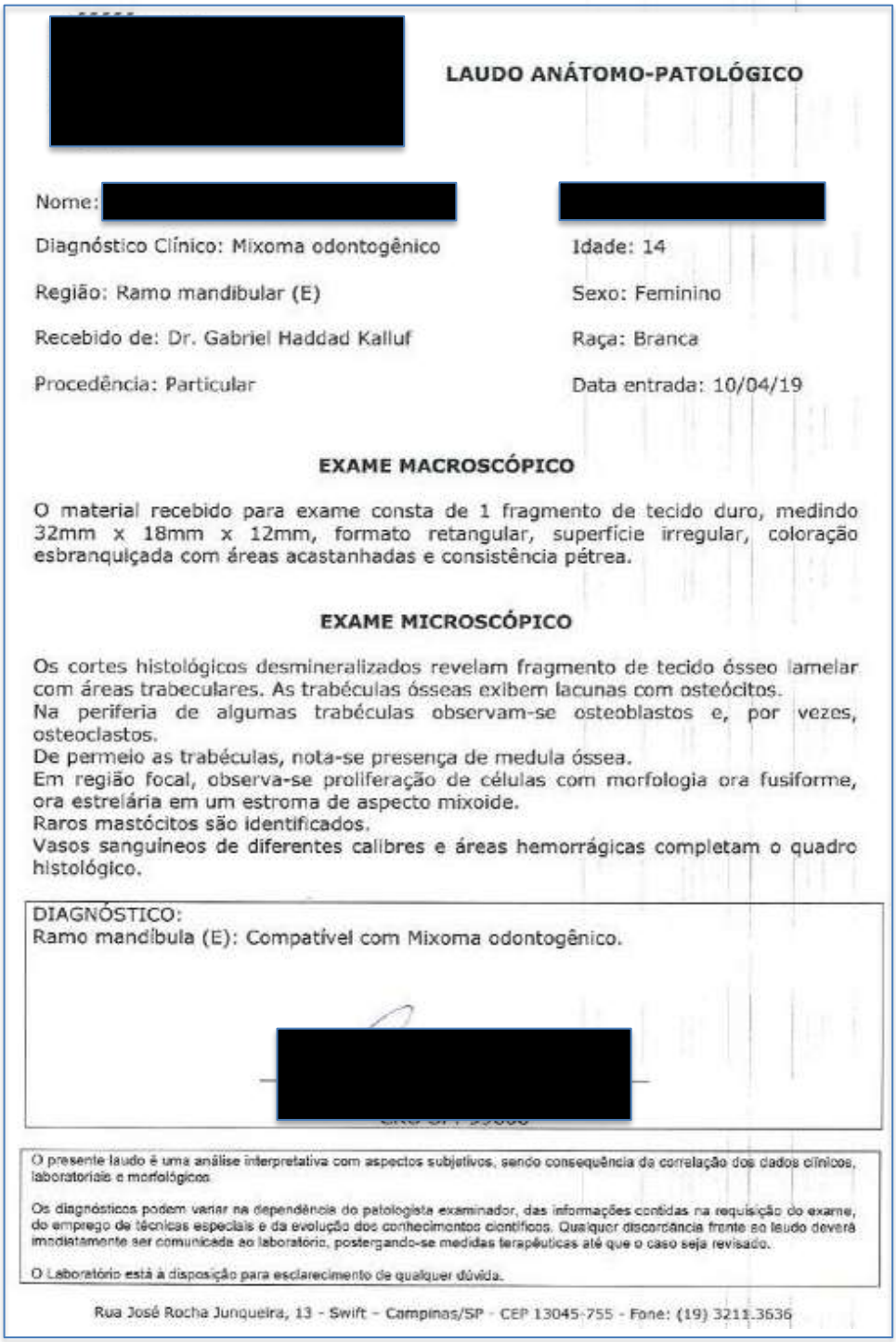
Cortes histológicos revelam tecido conjuntivo com áreas mixoides relacionadas a áreas de celularidade aumentada composta por elementos fusocelulares. Presença de edema, congestão e focos hemorrágicos, bem como focos de remodelação óssea. Não foi identificado epitélio escamoso ou queratinização nesta amostra.

EXAMES REALIZADOS NESTA INSTITUIÇÃO (Últimos 5 anos)

BIÓPSIA, SOE
MANDÍBULA, RAMO ESQUERDO
19/9/2017 P1743037 CISTO, SOE

APPENDIX 2

Macroscopic and microscopic examination report confirming the diagnosis. Case 1



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LAUDO ANÁTOMO-PATOLÓGICO

Nome: [redacted] [redacted]

Diagnóstico Clínico: Mixoma odontogênico | Idade: 14

Região: Ramo mandibular (E) | Sexo: Feminino

Recebido de: Dr. Gabriel Haddad Kalluf | Raça: Branca

Procedência: Particular | Data entrada: 10/04/19

EXAME MACROSCÓPICO

O material recebido para exame consta de 1 fragmento de tecido duro, medindo 32mm x 18mm x 12mm, formato retangular, superfície irregular, coloração esbranquiçada com áreas acastanhadas e consistência pétrea.

EXAME MICROSCÓPICO

Os cortes histológicos desmineralizados revelam fragmento de tecido ósseo lamelar com áreas trabeculares. As trabéculas ósseas exibem lacunas com osteócitos.
Na periferia de algumas trabéculas observam-se osteoblastos e, por vezes, osteoclastos.
De permeio as trabéculas, nota-se presença de medula óssea.
Em região focal, observa-se proliferação de células com morfologia ora fusiforme, ora estrelária em um estroma de aspecto mixoide.
Raros mastócitos são identificados.
Vasos sanguíneos de diferentes calibres e áreas hemorrágicas completam o quadro histológico.

DIAGNÓSTICO:
Ramo mandíbula (E): Compatível com Mixoma odontogênico.

[redacted]

O presente laudo é uma análise interpretativa com aspectos subjetivos, sendo consequência da correlação dos dados clínicos, laboratoriais e morfológicos.

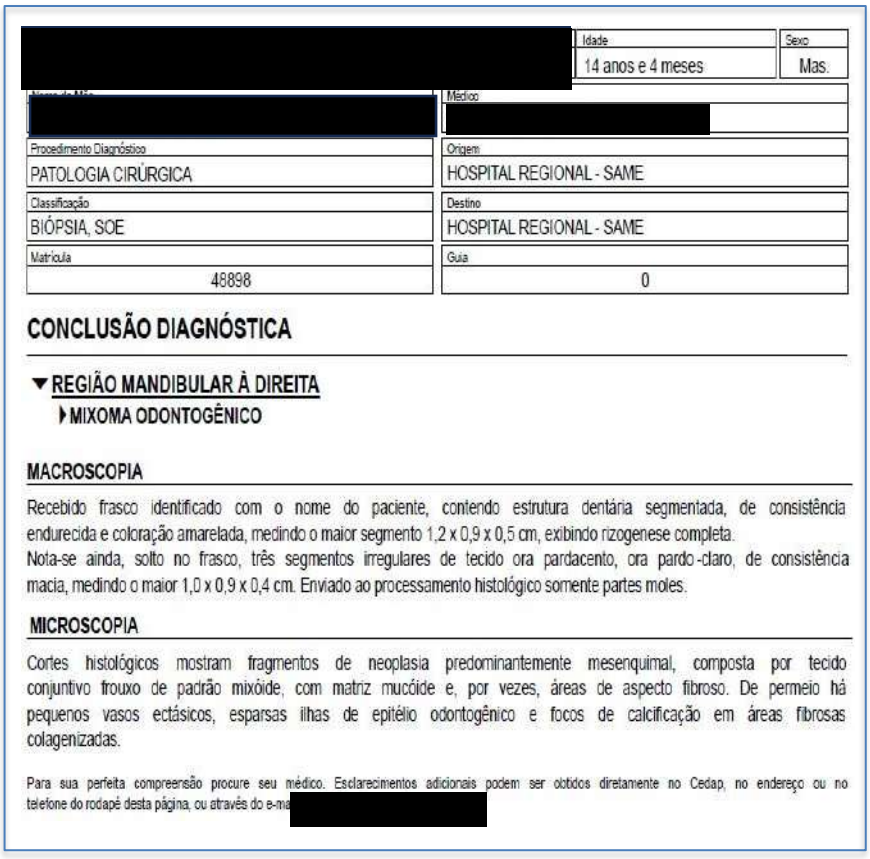
Os diagnósticos podem variar na dependência do patologista examinador, das informações contidas na requisição do exame, do emprego de técnicas especiais e da evolução dos conhecimentos científicos. Qualquer discordância frente ao laudo deverá imediatamente ser comunicada ao laboratório, postergando-se medidas terapêuticas até que o caso seja revisado.

O Laboratório está à disposição para esclarecimento de qualquer dúvida.

Rua José Rocha Junqueira, 13 - Swift - Campinas/SP - CEP 13045-755 - Fone: (19) 3211.3636

APPENDIX 3

Incisional biopsy report. Case 2



[redacted]	Idade: 14 anos e 4 meses	Sexo: Mas.
[redacted]	Médico: [redacted]	
Procedimento Diagnóstico: PATOLOGIA CIRÚRGICA	Origem: HOSPITAL REGIONAL - SAME	
Classificação: BIÓPSIA, SOE	Destino: HOSPITAL REGIONAL - SAME	
Matrícula: 48898	Guia: 0	

CONCLUSÃO DIAGNÓSTICA

▼ **REGIÃO MANDIBULAR À DIREITA**

▸ **MIXOMA ODONTOGÊNICO**

MACROSCOPIA

Recebido frasco identificado com o nome do paciente, contendo estrutura dentária segmentada, de consistência endurecida e coloração amarelada, medindo o maior segmento 1,2 x 0,9 x 0,5 cm, exibindo rizogenese completa.
Nota-se ainda, solto no frasco, três segmentos irregulares de tecido ora pardacento, ora pardo-claro, de consistência macia, medindo o maior 1,0 x 0,9 x 0,4 cm. Enviado ao processamento histológico somente partes moles.

MICROSCOPIA

Cortes histológicos mostram fragmentos de neoplasia predominantemente mesenquimal, composta por tecido conjuntivo frouxo de padrão mixóide, com matriz mucóide e, por vezes, áreas de aspecto fibroso. De permeio há pequenos vasos ectásicos, esparsas ilhas de epitélio odontogênico e focos de calcificação em áreas fibrosas colagenizadas.

Para sua perfeita compreensão procure seu médico. Esclarecimentos adicionais podem ser obtidos diretamente no Cedap, no endereço ou no telefone do rodapé desta página, ou através do e-ma[redacted]

APPENDIX 4

Macroscopic and microscopic examination report confirming the diagnosis. Case II

Nr Exame	Data de Cadastro	Nome do Paciente
P1334526	11/09/2013	[redacted]

Categoria	Data de Nascimento	Idade	Sexo
SUS- INTERNO-HOSP. INFANTIL	**27/02/1999**	14 anos e 7 meses	Mas.

Nome da Mãe	Médico
[redacted]	[redacted]

Procedimento Diagnóstico	Origem
PATOLOGIA CIRÚRGICA	HOSPITAL INFANTIL DR JESER AMARANTE FARIA

Classificação	Destino
BIÓPSIA, SOE	HOSPITAL INFANTIL DR JESER AMARANTE FARIA

Matrícula	Guia
843053	0

CONCLUSÃO DIAGNÓSTICA

REGIÃO MANDIBULAR À DIREITA

FIBROMIXOMA

Frasco 1).

DENTE, SOE

FIBROMIXOMA

Referente aos tecidos moles contidos no frasco 2).

NERVO, SOE

DENTRO DOS LIMITES DA NORMALIDADE

Frasco 3).

MANDÍBULA

REMODELAÇÃO ÓSSEA

Frasco 4).

MACROSCOPIA

Recebidos quatro frascos, identificados com o nome do paciente, seguindo a descrição e ordem apresentada nos frascos, constando de:

1) Porção alveolar (região mandibular à direita): Contém quatro fragmentos irregulares de tecido, de coloração pardo-variegada, consistência firme-elástica, medindo o maior 1,3 cm e o menor 0,7 cm. Todo o material foi remetido

MICROSCOPIA

1) Porção alveolar (região mandibular à direita): Cortes histológicos mostram neoplasia predominantemente mesenquimal, composta por tecido conjuntivo frouxo de padrão mixóide, com matriz mucóide e, por vezes, áreas de aspecto delicadamente fibroso. De permeio há esparsas ilhas de epitélio odontogênico e focos de calcificação,

2) 2° molar inferior direito: Cortes histológicos de partes moles anexas exibem a mesma lesão descrita acima, adicionado de algum tecido ósseo de arquitetura lamelar eutrófico. Em regiões focais da superfície óssea observam-se áreas de reabsorção, compatíveis com as lacunas Howship, que indicam atividade osteoclástica antiga.

3) Nervo alveolar inferior direito: Cortes histológicos revelam tecido conjuntivo frouxo, em meio ao qual há segmento de nervo periférico onde destacam-se fascículos neurais. Tais fascículos exibem estrutura preservada, recobertos por neuromísio íntegro, representado por endoneuro regular e perineuro rico em fibras colágenas. O compartimento endoneural contem fibras mielinizadas e núcleos de células de Schwann. Os vasos epineurais estão ectásicos e congestos e exibem paredes regulares. Áreas hemorrágicas, secundárias à manipulação cirúrgica, completam o