Universidad de Cuenca

Facultad de Odontología

Carrera de Odontología

“MIXOMA ODONTOGÉNICO. REVISIÓN DE LA LITERATURA”

Trabajo de titulación previo a la
obtención del título de Odontólogo

Autores:
Juan Francisco Pinos Pinos
Mateo Steven Sánchez Moscoso

Director:
María Fernanda Torres Calle
ORCID: 0000-0002-8097-212X

Cuenca, Ecuador
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Resumen

El propósito de este estudio es evaluar los aspectos demográficos como edad; localización; prevalencia; análisis clínico, radiográfico e histológico; el tratamiento, resultados y recurrencia del Mixoma Odontogénico. Esta revisión de la literatura fue llevada a cabo a finales de 2022 en diferentes motores de búsqueda (PubMed, Scielo, ProQuest y Google Scholar), usando la estrategia de búsqueda: (Mixoma odontogénico), (Mixofibroma odontogénico) y (Mixoma oral) (Tumor odontogénico) para identificar artículos que presenten información sobre las propiedades demográficas como edad; localización; prevalencia; análisis clínico, radiográfico e histológico; así como su tratamiento, resultados y recurrencia. De un total de 9.222 artículos encontrados en los motores de búsqueda únicamente 33 artículos cumplieron con los criterios de inclusión y exclusión. Con la revisión de la literatura llevada a cabo se concluyó que el mixoma odontogénico es considerado como el tercer tumor odontogénico más común. El cual, presenta una clara predilección por el sexo femenino, siendo poco frecuente en el sexo masculino y se encuentra mayormente entre la segunda y tercera década de vida. Su localización mayormente se encuentra en el sector posterior mandibular y clínicamente se manifiesta como un crecimiento lento, indoloro; aunque puede comportarse de forma más agresiva ocasionando dolor, parestesia y afección a estructuras adyacentes como dientes y huesos. Radiográficamente, el patrón más prevalente es de tipo multilocular, pero también se pueden encontrar patrones uniloculares o mixtos.

Palabras clave: mixoma odontogénico, mixofibroma odontogénico, mixoma oral, tumor odontogénico

Abstract

The purpose of this study is to evaluate demographic aspects such as age; location; prevalence; clinical, radiographic and histological analysis; The treatment, results and recurrence of Odontogenic Myxoma. This literature review was carried out at the end of 2022 in different search engines (PubMed, Scielo, ProQuest and Google Scholar), using the search strategy: (Odontogenic myxoma), (Odontogenic myxofibroma) and (Oral myxoma) (Odontogenic tumor) to identify articles that present information on demographic properties such as age; location; prevalence; clinical, radiographic and histological analysis; as well as its treatment, results and recurrence. Of a total of 9,222 articles found in the search engines, only 33 articles met the inclusion and exclusion criteria.**:** With the review of the literature carried out, it was concluded that odontogenic myxoma is considered the third most common odontogenic tumor. Which has a clear predilection for the female sex, being rare in the male sex and is found mostly between the second and third decade of life. Its location is mostly in the posterior mandibular sector and clinically it manifests as slow, painless growth; although it can behave more aggressively, causing pain, paresthesia and damage to adjacent structures such as teeth and bones. Radiographically, the most prevalent pattern is multilocular, but unilocular or mixed patterns can also be found.

Keywords: odontogenic myxoma, odontogenic myxofibroma, oral mixoma, odontogenic tumor

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1. Introduction

Odontogenic myxoma (OM) is a locally aggressive and infiltrative benign tumor that originates from the odontogenic ectomesenchyma, it is rare, according to the literature it manifests from 3 to 20%, however, it is considered the third most common odontogenic tumor after odontomas and ameloblastomas [1]. The World Health Organization (WHO) describes OM as a benign odontogenic neoplasm, characterized by stellate and spindle cells dispersed in an abundant myxoid extracellular matrix. They call it "odontogenic myxofibroma" when an increased amount of collagen is evident [2]. Patients mostly affected belong to the second and fourth decade of life, there is no sex predilection and it is most frequently observed in the mandible [1]. This tumor has an incidence of approximately 0.07/1,000,000 inhabitants, represents about 3.3-15.7% of odontogenic tumors in adults and about 8.5-11.6% of odontogenic tumors in children [3].

OM manifests variable radiological and clinical presentations, so its diagnosis should be exhaustive based on clinical, radiological and histopathological examinations. Clinically, OM is characterized by slow growth that can cause local bone destruction, cortical expansion, soft tissue infiltration, resorption and tooth movement. The evolution of OM is characterized as slow, insidious and asymptomatic [4].

Radiographically its appearance is somewhat variable, as this can range from unilocular to multilocular radiolucency with multiple loculation patterns (4) that may or may not have clearly defined borders [1]. OMs containing multilocular radiographic patterns can vary in appearance, among these variations include "soap bubble", "honeycomb" and "tennis racket", "sunburst" or "sunburst" shapes that may suggest destructive and expansive behavior of this lesion [4].

In histological studies the odontogenic myxoma is observed to be composed of stellate to spindle-shaped cells wrapped in an abundant extracellular matrix rich in mucin, without encapsulation and that may contain epithelial debris; in some cases the matrix may present collagen bundles that give it the denomination of myxofibroma [1, 4].

Treatment is variable and depends on the size of the lesion. There are conservative treatments focused on curettage and enucleation of the lesion, although the most widely accepted approach is radical resection with wide margins to avoid high recurrence [5-7]. The present article aims to evaluate demographic aspects such as age; location; prevalence; clinical, radiographic and histologic analysis; treatment, outcome and recurrence.

2. Materials and methods.

2.1 Inclusion and exclusion criteria:

A total of 32 articles were included in the present review based on the level of evidence

including systematic reviews, literature reviews with case reports, case series. Each of these had to have a full-text article in English or Spanish. On the other hand, we excluded articles published outside the last 20 years, and articles such as expert opinions, experimental studies and editorials, based on the levels of scientific evidence (Figure 1).

2.2 Search strategy:

An extensive electronic search of scientific articles published between January 2002 through December 2021 was performed in PubMed, SciELO, Proquest, and Google Scholar databases. The following search terms were used: "oral myxoma", "odontogenic myxoma" and "odontogenic myxofibroma". (Figure 1). In addition, duplicate articles were removed manually and using the bibliographic manager (Zotero).

2.3 Data extraction and evaluation:

Only data relevant to the study were extracted such as: demographic data (age, sex), prevalence, location (maxilla or mandible), clinical, radiographic and histopathologic features, its treatment (conservative or radical) and recurrence rate.

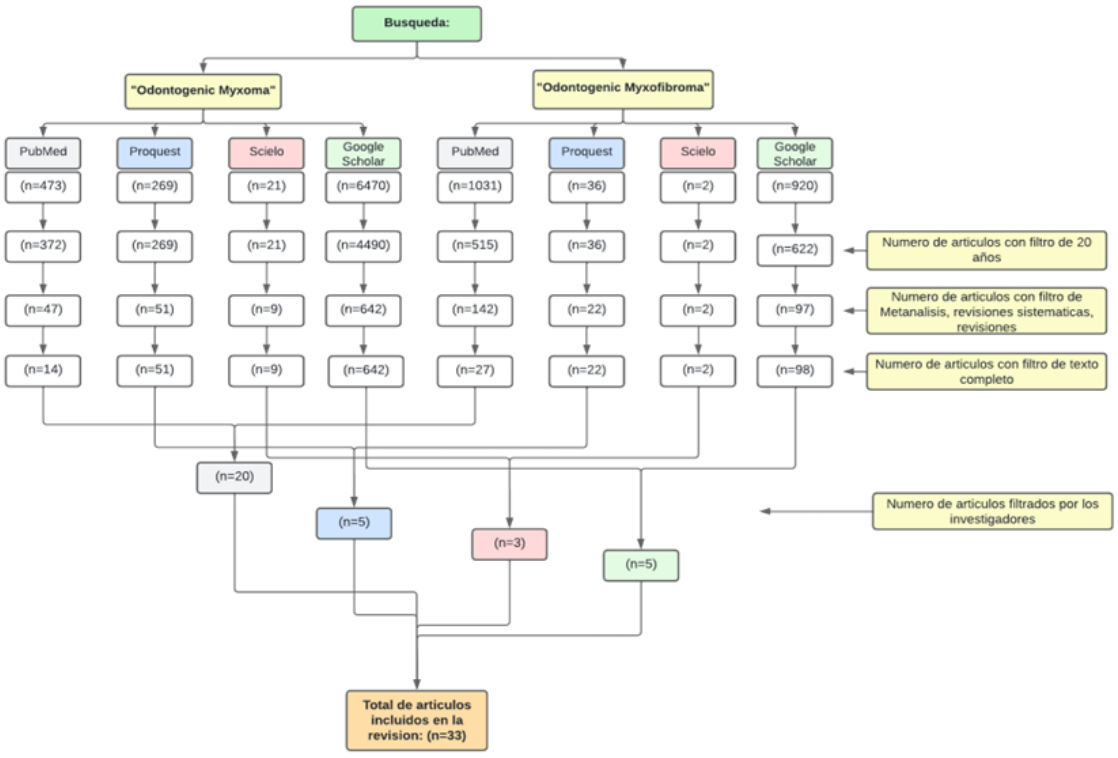

Figure 1. Search tree
Authors

3. Results

3.1. Age and sex:

The results of a large number of studies were compared with regard to demographic characteristics such as age and sex. Regarding age, the usual age of onset of OM is considered to be between the first and fourth decade of life [1, 5, 8]. However, it is also usual to find it between the second and third decade of life [8-10]. The information obtained is variable. According to Kawase et al. 50% of the cases correspond to the male sex, and 50% to the female sex, showing a 1:1 ratio between both sexes [12]. However, Sohrabi et al. indicate that women are the most affected with a ratio of 1.5:1 [4].

3.2. Prevalence:

The prevalence of OM is variable depending on the geographic area, as in America, Asia and Europe frequencies from 0.5% to 17% have been reported [8, 13, 14], while in African countries we found prevalences of 10.3% and 19% [15]. The prevalence rates of MO are relatively low, however, OM is considered to be the third most common odontogenic tumor [16, 17].

3.3. Location:

The literature demonstrates a clear prevalence of OM in the posterior mandibular sector [1, 6, 12, 13, 18, 19]. Authors such as Tavakoli et al. indicate a 3:4 maxillary-mandibular ratio [7]. Although it is not exclusive to this area.

3.4. Clinical features:

The lesion initially manifests painless slow growth with expansion of the cortical bone [6], although more aggressive behavior may also be evidenced; causing pain, ulcers, paresthesia, displacement and resorption of adjacent structures such as teeth and bone [5, 20]. According to Sohrabi et al. and Leong et al. 75% of OM present signs of cortical perforation, 20% present root resorption and 58.6% manifest tumefaction causing facial asymmetry [4, 21].

3.5. Radiographic features:

The radiographic patterns of OM are well known for their characteristic appearance. Radiographic patterns range from unilocular (Figure 2) to multilocular, the latter being the most prevalent [16, 22, 23]. White et al; adds that multilocular patterns are characterized by a "honeycomb", "soap bubble" or "tennis racket" appearance [24].

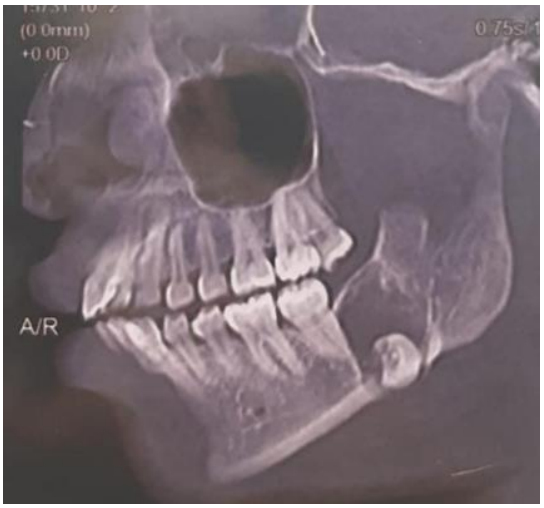

Image courtesy. Sarmiento Sánchez L[1] . OM CBCT sagital view [Universidad de Cuenca].2023 [Cited January 5, 2023].

Figure 2: Tomographic study, sagittal OM view. There is a well-defined unilocular radiolucent image in the posterior sector of the mandible associated with a retained and displaced dental organ, compatible with Odontogenic Myxoma.

3.6. Histopathology:

OM are generally made up of loosely arranged spindle or stellate cells with long fibrillar processes that are intertwined within remnants of quiescent odontogenic epithelium, embedded in an abundant myxoid or mucoid extracellular matrix abundant in hyaluronic acid (Figure 3) [4, 8, 9, 14, 16, 25, 26]. In addition, it is common to find calcifications, bone trabeculae and blood capillaries arranged within the mucoid material; and in certain cases large amounts of collagen are observed arranged in the form of fibers, which gives the characteristic name of myxofibroma or fibromyxoma (Figure 4) [6, 8, 18, 27].

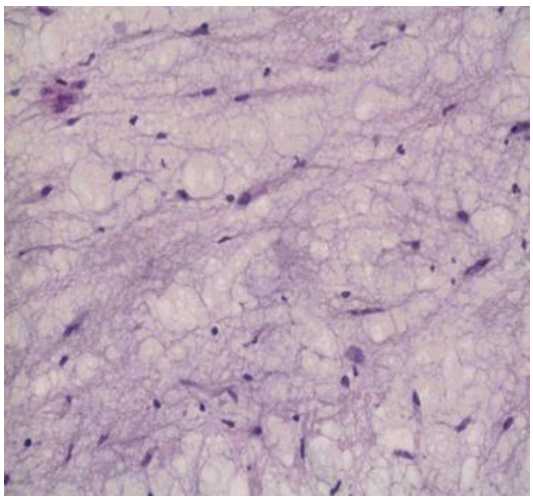

Image courtesy. Torres Calle M. OM histology with 400x magnification [Universidad de Cuenca].2023 [Cited January 5, 2023].

Figure 3: Conventional OM histologic image. Freely arranged spindle cells are observed, showing long intertwining fibrillar processes, enveloped in an abundant myxoid extracellular matrix located in the extensive extracellular spaces. There are few collagenous bundles or fibers (H&E 400x stain).

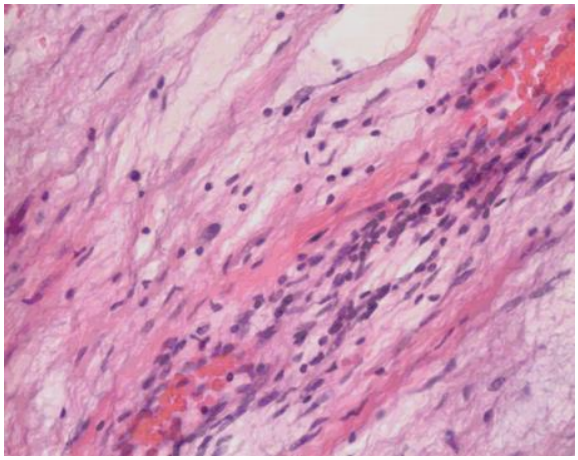

Image courtesy. Torres Calle M. OM histology with 400x magnification [Universidad de Cuenca].2023 [Cited January 5, 2023].

Figure 4: Histologic image of myxofibroma. Spindle cells are observed freely arranged in an abundant myxoid extracellular matrix with abundant collagenous bundles or fibers (H&E 400x stain).

3.7. Treatment:

There are several treatment modalities for OM ranging from conservative surgery which could be either enucleation, curettage or curettage [5, 18], to more invasive treatments such as segmental resection or in bloc resection [16]. Treatment with radiotherapy should not be considered as a standard therapy [28].

3.8. Recurrence:

Recurrence of this tumor is high, with percentages fluctuating between different values as various authors indicate a recurrence rate of 25% [4, 5, 9, 16, 24, 28].

4. Discussion:

Authors such as Dotta et al., Shivashankara et al., Bisla et al., and others consider the usual age of onset of OM to be between the first and fourth decade of life [1, 5, 8, 25, 29, 30].

However, Chrcanovic et al., Manne et al., Sohrabi et al. and other authors indicate that there is a greater predilection for onset between the second and third decade of life [4, 9-11, 13, 18, 21, 22, 24, 28]. On the other hand, Wang et al. indicate a higher incidence in patients in the second and fifth decade of life [23]; and Hammad et al. extend the age range of onset from the first year to 73 years [31]. Regarding sex predilection, Kawase et al. indicate that 50% of the cases correspond to the male sex and 50% to the female sex, showing a 1:1 ratio between the sexes; which corresponds to the results of White et al. and Priya et al. which indicate that there is no established sex predilection [12, 24, 28]. On the other hand, Godishala et al. report a clear female sex predilection [32]. This is in agreement with other authors such as Sohrabi et al. who report that females are the most affected with a 1.5:1 ratio [4]. Likewise, Wang et al. obtains a female predilection with a 2:1 ratio compared to the male sex [23]. Saalim et al. report a higher ratio of 2.2:1 for the female sex [29]. Titinchi et al. show the highest ratio of 2.6:1 for the male sex [25].

The prevalence of OM is highly variable, so that in America, Asia and Europe, frequencies from 0.5% to 17.7% have been reported according to Bisla et al., Manne et al. and Vasconcelos et al [8, 13, 14]. This is in contradiction with the results of Godishala et al. which indicate prevalences from 0.04 % to 3.7 % [32]. On the other hand, Ghazali et al. document prevalences of 10.3% and 19% in countries belonging to the African continent [15]. In Latin America, Tapia et al. report an approximate incidence of 0.07/1,000,000 inhabitants, which represents about 3.3-15.7% of the population, which is relatively consistent with Bisla [3]. MO is considered the third most frequent odontogenic tumor, behind Odontomas and Ameloblastomas, statistically representing 3-6% of all odontogenic tumors according to Sohrabi et al., Saalim et al. and other authors [4, 10, 23, 26, 29].

OM can be located in different places in the maxilla or mandible. Leong et al. report that 66.4% of OM occur in the mandible and 33.6% in the maxilla [21]. Dotta et al. report a higher prevalence of OM in the mandibular posterior sector with 59.48%, followed by the maxilla in the posterior region with 52.28%, the maxillary anterior region with 19.65% and finally the mandibular anterior region with 16.23% [1]. Chrcanovic et al., Kawase et al., Bannaser et al., Manne et al., Noffke et al. reported that OM is most frequently located in the mandible in the posterior sector [6, 12, 13, 18, 19] which agrees with Benjelloun et al. [33]. Bisla et al., found that the location of MO was in the anterior region of the maxilla [8]. Tavakoli et al. reported a 3:4 maxillary-mandibular ratio [7]. Tapia et al. mentioned a more frequent general location in the mandible and a maxillary location in pediatric patients under 2 years of age [3] (Anexo A).

In relation to the clinical characteristics of OM, Banasser et al, Tavakoli et al, Tapia et al, and Kornecki et al, in their studies mention that the lesion presents a painless slow growth with

expansion of the cortical bone [3, 6, 7, 17], this agrees with results obtained from Takahashi et al, and Wanget al., [11, 23]; while Shupack et al. and Shivanskara et al. consider that the lesion may behave more aggressively; causing pain, ulcers, paresthesia, displacement and resorption of adjacent structures such as teeth and bone [5, 13, 20]. According to Titinchi et al., Tavakoli et al., Ghazali et al., and Leong et al., 58.6% of lesions manifest tumefaction causing facial asymmetry that slowly increases to the affected jaw [7, 15, 21, 25].

The radiographic characteristics of OM are variable. Dotta et al., yields results indicating that the multilocular pattern is found in 57.49%, followed by the unilocular pattern with 32.87% and finally the mixed appearance with 9.64% [1]. Vasconcelos et al. similarly found a predominance of multilocular appearance with 61.5%, while unilocular lesions corresponded to 34.5% and finally mixed appearance lesions only reached 4% [14]. Titinchi et al. in their study found that 77.7% of mandibular myxomas were multilocular and 36.4% of maxillary myxomas were multilocular. In contrast to unilocular mandibular myxomas 16.7% and unilocular maxillary myxomas 45.5% in their radiographic appearance, 2 cases were not diagnosed in the maxilla and 1 case in the mandible [25]. Banasser et al. indicated a percentage of 28.9% for multilocular radiolucent lesions and 21.1% in unilocular radiolucent lesions [6]. Kheir et al. found 6.7% in unilocular lesions and 43.3% in multilocular lesions [22]. Martins et al. found that multilocular lesions were 54% and were not found with root resorption [9]. According to Kauke et al. and Wang et al. radiographic patterns range from unilocular to multilocular, the latter being the most prevalent [16] which is in agreement with the results of Thomas et al. and Pereira et al, [28, 30]. Tapia et al., found multilocular lesions, however, they can also be found as unilocular lesions that are characterized by being well demarcated with ranges ranging from approximately 1-13cm [3]. White et al. and Wang et al. describe that multilocular patterns are characterized by having a "honeycomb", "soap bubble" or "tennis racket" appearance [23, 24] (Anexo B).

Histologically, Bisla et al. in their studies describe the OM as a collection of scattered pleomorphic cells with calcifications, bony trabeculae, blood vessels, all enveloped within a mucinous matrix [8]. Sohrab et al, indicates the presence of stellate, spindle-shaped cells that present long fibrillar processes that tend to intertwine with the inactive odontogenic epithelium dispersed throughout the myxoid ground substance; such description agrees with Titinchi et al, Martins et al, Godishala et al, Thomas et al, Leong et al, and Takahashi et al, [4, 9, 11, 21, 25, 28, 32]. The study by Francisco et al. describes the presence of abundant dense collagen fibers with some mitotic figures and binucleated cells, with the presence of minimal vascularization [27]. Tapia et al., on the other hand, indicate the presence of mast cells and plasmacytes [3]. While Reverand et al. mention that the mucoid or myxoid stroma is composed of abundant content of mucopolysaccharides, such as hyaluronic acid and chondroitin sulfate

[26]. Finally, in certain cases, large amounts of collagen are observed arranged in the form of fibers, which gives the characteristic name of myxofibroma or fibromyxoma [8, 18, 27]. Thus, Banasser et al. in their retrospective study of 38 cases indicate a prevalence of 79% of cases of conventional odontogenic myxomas and 21% correspond to myxofibromas in histopathological specimens [6] (Anexo C)

Generally, the treatment of OM is classified into conservative including (curettage, enucleation with curettage, excision curettage and excision) and bloc resection, according to Saalim et al. and Kauke et al [16, 27]. Martins et al. mention that treatment ranges from conservative enucleation and curettage to in bloc resection and hemimandibulectomy [9]. Shivashankara et al. state in their study that the treatment for OM is conservative surgery [5]. Chrcanovic et al, reported that conservative surgery treatment was used in 44.3% of cases and radical surgery in 55% of cases and 0.7% by radiotherapy or no treatment. [18]. Thomas et al. mention excision, enucleation and curettage with and without electrical or chemical cauterization, bloc resection and wide resection with and without immediate grafting as treatments, on the other hand, they mention that radiotherapy should not be considered as a standard treatment option [28]. Tavakoli et al. also indicate that the treatment of OM varies from enucleation to radical resection and that it is advisable to start treatment with the most conservative options and gradually advance to more aggressive treatment options only if there is recurrence [7]. Wang et al. agree with the various authors that radical therapy is essential as a treatment when a lesion with locally aggressive behavior is encountered [23]. Takahashi et al. mentions that the only treatment for OM is surgery and enucleation alone is an inadequate treatment [11]. On the other hand, Sohrabi et al. mentions resection for OM larger than 3 centimeters, and enucleation and curettage for smaller lesions [4]. The correct treatment for OM according to Kornecki et al. is radical surgical resection with 1 cm safety margins [17].

Finally, recurrence of OM is also highly variable, with Shivashakara et al., Kauke et al., Thomas et al. and White et al. reporting a recurrence rate of 25% [5, 16, 24, 28]. Sohrabi et al. also agree with the very high recurrence of 25% but indicate that only after enucleation and curettage [4]. Martins et al. agrees with the mean rate of 25% and adds that the rates decrease from 24% to 8.3% in patients who were treated conservatively and accompanied with a follow-up of more than 60 months [9]. In contrast to the above Dotta et al. mentions a recurrence of 13.04% of cases in both conservative and radical surgery. [1]. Saalim et al. agree with the overall recurrence of 13%, with a mean follow-up of 10 years in the cases observed [29]. Also, recurrence of OM will depend on the treatment as indicated by Banasser [6]. On the other hand, Francisco et al. in their study observed that patients showed recurrence and required additional surgery in 30% when previously treated with curettage and in 25% when treated with resection as the initial procedure [27]. Vasconcelos et al. reported in their follow-up of 136 cases, only 5 cases with 3.7% reported recurrence [14]. Tapia et al. in their study in pediatric

patients found that no patient treated with conservative therapy presented recurrence, this demonstrated the safety of conservative surgical treatment in children [3]. Reverand et al., states that the recurrence of OM is probably due to the fact that they are non-encapsulated lesions whose myxomatous cells can infiltrate the adjacent bone [26]. Finally, Pereira et al. report that the recurrence rate of OM is not associated with radiographic features, location, presence of bone expansion and cortical perforation [30] (Anexo D).

5. Conclusion:

In conclusion, odontogenic myxoma is a rare pathologic entity, despite this, it is considered the third most common odontogenic tumor. Its etiopathogenesis is not very clear. Demographically, there is a clear predilection for the female sex, being infrequent in the male sex and it is mostly found between the second and third decade of life. Its location is mostly in the posterior mandibular sector and clinically it manifests as a slow, painless growth, although it can behave more aggressively causing pain, paresthesia and involvement of adjacent structures such as teeth and bones. Radiographically, the most prevalent pattern is multilocular, but unilocular or mixed patterns can also be found. Regarding prognosis and recurrence, these are closely linked to their treatment, however, there is no "gold standard" for the therapy and diagnosis of the lesion, so more studies are needed to establish a fixed guideline for its treatment.

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Anexos

Anexo A: Results of the review variables: age, sex, prevalence, location

number	Author	Year	Age	Sex	prevalence	Location
1	Dotta et al.	2020	Range 8-40 years	F	-	Posterior Mandibular (59.48%) Anterior Mandibular (16.23%). Posterior Maxilla: (52.28%), Anterior Maxilla (19.65%)
2	El-Naggar	2017	-	-	-	-
3	Tapia et al.	2021	third decade	F	0.07/1,000,000 - 3.3-15.7% adults 8.5-11.6% in children	General mandibular and maxillary in children under 2 years of age
4	Sohrabi et al.	2021	Between 23 and 30 years old	F 1.5:1	3%–6% total neoplasms	Mandibular: posterior body, ramus and angle.
5	Shivashankara et al.	2017	10 - 40 years	F 2:1	0.5% to 19%	mandibular
6	Banasser et al.	2020	Range 6-84 years	F	39.50%	Mandibular 60.5%, Maxillary 39.4%
7	Tavakoli et al.	2019	61 years	-	-	Maxillary-Mandibular 3:4
8	Bisla et al.	2020	10 and 40 years	F 1.5:1	0.5% to 17.7%	anterior maxilla
9	Martins et al.	2021	Second and third decade	no predilection	-	Posterior mandibular (77%) and maxilla (23%)
10	Singh et al.	2018	Second and third decade	-	3%–6% total neoplasms	mandibular
eleven	Takahashi et al.	2018	Second and third decade	F 2:1	0.5 to 20%	-
12	Kawase-Koga et al.	2014	Average age of 31.9 years	F 1:1	.	Posterior Mandibular
13	Manne et al.	2012	Age. 22.7 - 36.9 years	-	0.5% and 17.7%	mandibular
14	Vasconcelos et al.	2017	Mean age 30.7 years	F	0.5 and 17.7%	Mandibular 514 cases (52.9%) and Maxillary 458 (47.1%)
fifteen	Ghazali et al.	2021	-	F	l 10.3% and 19% (Africa)	mandibular
16	Kauke et al.	2018	Median age 35 years	-	3 or 4 frequent tumor	Jaw: 32 Jaw: 12
17	Kornecki et al.	2015	third decade of life	-	3rd frequent tumor	posterior mandible

18	Chrcanovic et al.	2018	Age range 28.6 years	F	-	Mandibular: 1261 Maxilla: 344 cases
19	Noffke et al.	2007	-	F	-9.10%	Jaw: 19 Jaw: 11
twenty	Shupak et al.	2020	-	-	-	-
twenty-one	Leong et al.	2010	Second or third decades	-	-	Mandibular 66.4%, Maxillary 33.6%
22	Kher et al.	2013	Second and third decade	F	-	-
23	Wang et al.	2017	Second and fifth decades	F 2:1	3%–6% total neoplasms	Mandibular, mandibular ramus
24	White et al.	2020	Ages 25 to 30 years	no predilection	-	posterior mandible
25	Titinchi et al.	2016	Range of 7 and 44 years	P 2.6:1	-	Mandible: 62.1% Maxilla: (37.9%)
26	Reverand et al.	2018	third decade	-	3%–6% total neoplasms	mandibular
27	Francis et al.	2017	Ages between 7 and 51 years	F	-	Mandibular (11 cases, 78.57%)
28	Thomas et al.	2011	-	no predilection	2nd common tumor	mandibular
29	Salim et al.	2019	Fourth decade of life, ages 7 and 55 years	F 2.2:1	3%–6% total neoplasms	Jaw: 30 Jaw: 9
30	Pereira et al.	2019	Second and fourth decade	-	-	mandibular
31	Hammad et al.	2016	Range 1-73 years	-	-	-
32	Godishala et al.	2018	-	F	0.04% to 3.7%	-
33	Benjelloun et al.	2017	Second or third decades	F	-	mandibular

Anexo B: Variable revision results: clinical and radiographic characteristics

number	Author	Year	Clinical features	Radiographic features
1	Dotta et al.	2020	-	Multilocular (57.49%), Unilocular (32.87%) Mixed appearance (9.64%)
2	El-Naggar	2017	-	-
3	Tapia et al.	2021	Slow growth, asymptomatic, cortical expansion bone and dental displacements	Multilocular or Unilocular; well defined, ranges between 1-13 cm.
4	Sohrabi et al.	2021	75%: cortical bone perforation, 20%: root resorption	Multilocular 62.9%

5	Shivashankara et al.	2017	Pain, paresthesia, ulceration, mobility	Multilocular or Unilocular
6	Banasser et al.	2020	Slow and painless growth, cortical expansion and root divergence.	Multilocular 28.9% or Unilocular 21.1%
7	Tavakoli et al.	2019	Painless swelling, slow growth, displacement of teeth.	Multilocular or Unilocular
8	Bisla et al.	2020	Root resorption and displacement of teeth.	unilocular
9	Martins et al.	2021	-	Multilocular 54%, without root resorption
10	Singh et al.	2018	marked asymmetry	Unilocular or Multilocular margins well defined or diffuse.
11	Takahashi et al.	2018	No pain and no hypoesthesia	Maxillary Uniloculars and Mandibular Multiloculars.
12	Kawase-Koga et al.	2014	-	-
13	Manne et al.	2012	Intermediate pain, and more aggressive	Multilocular “soap bubble”
14	Vasconcelos et al.	2017	Displacement of teeth, rarely seen root resorption.	Multilocular: 61.5%, Unilocular: 34.5%, Mixed Appearance 4%
15	Ghazali et al.	2021	Swelling was the most common clinical complaint	Multilocular or Unilocular
16	Kauke et al.	2018	Dental resorption, dental deviation and cortical perforation	Multilocular: 28, Unilocular 16
17	Kornecki et al.	2015	asymptomatic	Multilocular or Unilocular
18	Chrcanovic et al.	2018	53.8% dental displacement, 75% cortical perforation, 20% root resorption	Multilocular 62.9%
19	Noffke et al.	2007	-	Multilocular: 24, Unilocular 6
20	Shupak et al.	2020	Displacement or resorption of nearby structures.	
21	Leong et al.	2010	Swelling or asymmetry	multilocular
22	Kher et al.	2013	-	Multilocular 43.4%, Unilocular 6.7%
23	Wang et al.	2017	painless swelling with facial asymmetry	Multilocular or Unilocular, mixed appearance of honeycomb and tennis racket patterns.
24	White et al.	2020	asymptomatic	Unilocular, Multilocular “honeycomb”, “soap bubble” or “tennis racket”
25	Titinchi et al.	2016	31%: painful, 58.6%: history of swelling	Mandibular multilocular: (77.7%) Maxillary multilocular: (36.4%) Mandibular unilocular: (16.7%) Maxillary unilocular: (45.5%)
26	Reverand et al.	2018	Slow growth, pain, paresthesia, ulceration and dental mobility	multilocular
27	Francis et al.	2017	Swelling, cortical perforation, dental mobility and pain	Multilocular: 64.3%
28	Thomas et al.	2011	Swelling	multilocular

29	Salim et al.	2019	-	Multilocular: 30, Unilocular 7
30	Pereira et al.	2019	Facial deformities and tooth loss	multilocular
31	Hammad et al.	2016	Swelling, cortical perforation, dental mobility and pain	Multilocular or Unilocular
32	Godishala et al.	2018	painless	multilocular
33	Benjelloun et al.	2017	-	-

Anexo C: Variable review results: histopathology

number	Author	Year	histopathology
1	Dotta et al.	2020	93.43%: conventional microscopy
2	El-Naggar	2017	-
3	Tapia et al.	2021	Stellate cells in myxoid stroma, with collagen fibers, odontogenic epithelium, mast cells and plasma cells.
4	Sohrabi et al.	2021	Stellate cells with scattered fibrillar processes in myxoid ground substance
5	Shivashankara et al.	2017	Conventional microscopic findings plus remnants of epithelium
6	Banasser et al.	2020	79%: conventional microscopy, 21%: myxofibroma microscopy
7	Tavakoli et al.	2019	-
8	Bisla et al.	2020	Pleomorphic cells, connective tissue fibers, calcifications, bony trabeculae in a mucinous matrix.
9	Martins et al.	2021	Myxoid connective tissue stroma with few collagen fibers with spindle and round cells
10	Singh et al.	2018	Round and angular cells found in the abundant mucoid stroma
11	Takahashi et al.	2018	Stellate cells in a loose myxoid stroma with few collagen fibers
12	Kawase-Koga et al.	2014	-
13	Manne et al.	2012	Conventional histopathologic features
14	Vasconcelos et al.	2017	Round and angular cells in abundant mucoid stroma
15	Ghazali et al.	2021	-
16	Kauke et al.	2018	Spindle cells in an abundant myxoid or mucoid extracellular matrix
17	Kornecki et al.	2015	spindle cells in a myxoid stroma
18	Chrcanovic et al.	2018	conventional histopathology, but with angular septa
19	Noffke et al.	2007	-
20	Shupak et al.	2020	-
21	Leong et al.	2010	Spindle and stellate cells arranged with fibrillar processes
22	Kher et al.	2013	-

23	Wang et al.	2017	Myxoid or mucoid extracellular matrix, without capsule
24	White et al.	2020	Stellate cells with long pale cytoplasmic processes
25	Titinchi et al.	2016	Stellate to spindle cells in a mucoid-rich intercellular matrix
26	Reverand et al.	2018	Spindle cells scattered in a mucoid stroma abundant in mucopolysaccharides
27	Francis et al.	2017	Conventional microscopy rarer mitotic figures or binucleate cells, without encapsulation
28	Thomas et al.	2011	Spindle and star-shaped cells arranged in mucoid-rich stroma
29	Salim et al.	2019	-
30	Pereira et al.	2019	spindle or star-shaped cells scattered in a myxoid matrix.
31	Hammad et al.	2016	Conventional histopathology plus calcified trabeculae
32	Godishala et al.	2018	Plump, stellate cells in a myxoid matrix with delicate collagen fibers.
33	Benjelloun et al.	2017	-

Anexo D: Variable review results: treatment, recurrence

number	Author	Year	Treatment	recurrence
1	Dotta et al.	2020	surgical resection	13.04%
2	El-Naggar	2017	-	-
3	Tapia et al.	2021	The standard surgical treatment is resection with safety margins.	None
4	Sohrabi et al.	2021	Resection: greater than 3 centimeters, Enucleation, curettage: minor injuries.	25% after enucleation and curettage
5	Shivashankara et al.	2017	conservative surgery	25%
6	Banasser et al.	2020	Curettage, enucleation and peripheral osteotomy	31% conservative curettage, 13.1% enucleation
7	Tavakoli et al.	2019	Enucleation, radical resection: it is advisable to start the treatment with the most conservative options and gradually use the most aggressive options only if there is a recurrence.	-
8	Bisla et al.	2020	conservative surgery	At 2 years of follow-up
9	Martins et al.	2021	Conservative enucleation, curettage, en bloc resection, hemimandibulectomy	25%, decreased from 24% to 8.3% in patients treated conservative with a 60-month follow-up
10	Singh et al.	2018	Excision with narrow margins or curettage, surgical treatment	fifteen%

11	Takahashi et al.	2018	Surgery. Enucleation alone is inadequate.	Conservative treatment from 10% to 33%
12	Kawase-Koga et al.	2014	Conservative surgical techniques and radical treatment	No recurrences in radical surgery.
13	Manne et al.	2012	Radical treatment of en bloc resection	-
14	Vasconcelos et al.	2017	Conservative treatment	3.70%
15	Ghazali et al.	2021	-	-
16	Kauke et al.	2018	Conservative (enucleation, curettage and marginal resection) or radical (segmental, en bloc resection)	25%
17	Kornecki et al.	2015	Radical surgical resection with 1 cm safety margins	High recurrence rate.
18	Chrcanovic et al.	2018	Conservative surgery: 44.3%; Radical surgery: 55%	44 recurrences
19	Noffke et al.	2007	-	-
21	Shupak et al.	2020	(75%) mandibular resections, (25%) conservative treatments.	Recurrence 9 years after enucleation and curettage
21	Leong et al.	2010	Local excision, curettage, enucleation, radical resection	Conservative surgery produces greater recurrence.
22	Kher et al.	2013	-	-
23	Wang et al.	2017	Radical therapy when it is a locally aggressive behavior	High recurrence rate.
24	White et al.	2020	Curettage: small lesions Resection: large lesions	25%
25	Titinchi et al.	2016	-	-
26	Reverand et al.	2018	curettage, radical excision	Unencapsulated lesions can infiltrate adjacent bone.
27	Francis et al.	2017	Curettage 71.4% or segmental resection 28.6%	Recurrences in curettage 30% and 25% resection.
28	Thomas et al.	2011	Excision, enucleation and curettage with and without electrical or chemical cauterization, en bloc resection and wide resection with and without immediate grafting, radiotherapy should not be considered as standard therapy.	General rates 10 and 33%, average rate of 25%
29	Salim et al.	2019	Conservatives (curettage, enucleation with curettage, excision curettage and excision) and resection.	13% 10-year follow-up
30	Pereira et al.	2019	Enucleation followed by peripheral osteotomy	It is not associated with location, the presence of bone expansion, cortical

				perforation, and radiographic features.
31	Hammad et al.	2016	-	-
32	Godishala et al.	2018	Enucleation, curettage or en bloc resection.	High recurrence rate.
33	Benjelloun et al.	2017	-	-