UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE ODONTOLOGIA

LARISSA DILL FUCKS

MUCINOSE ORAL FOCAL: UMA REVISÃO SISTEMÁTICA

Porto Alegre
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Trabalho de Conclusão de Curso apresentado ao Curso de Odontologia da Universidade Federal do Rio Grande do Sul, como requisito parcial para obtenção do título de Cirurgião-Dentista.

Orientador: Profª Drª Manoela Domingues Martins

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Porto Alegre, 29 de Março de 2023.

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"[...] Sempre antes de realizar um sonho, a Alma do Mundo resolve testar tudo aquilo que foi aprendido durante a caminhada. Ela faz isto não porque seja má, mas para que possamos, junto com o nosso sonho, conquistar também as lições que aprendemos seguindo em direção a ele. É o momento em que a maior parte das pessoas desiste. É o que chamamos, em linguagem do deserto, de "morrer de sede quando as tamareiras já apareceram no horizonte"."

Paulo Coelho – O Alquimista

RESUMO

A mucinose oral focal (MOF) é uma lesão benigna, que acomete a cavidade bucal, mas sua exata etiologia permanece desconhecida. A MOF é uma lesão rara, sendo descrita na literatura pela primeira vez em 1974 pelo Dr. Tomich e seus colaboradores, considerada uma contraparte de mucinose cutânea focal. Visto os poucos relatos na literatura, uma revisão sistemática agrupando os casos de MOF, seria importante para elucidar os atuais conhecimentos sobre essa lesão. O objetivo deste estudo foi integrar as características demográficas, clínicas e histopatológicas de casos previamente publicados de MOF em uma revisão sistemática. A revisão foi devidamente registrada no PROSPERO. Foram realizadas buscas eletrônicas sem restrição de data de publicação nas seguintes bases de dados: Embase (Elsevier), PubMed/MEDLINE (National Library of Medicine), Web of Science (Thomson Reuters) e Scopus (Elsevier). Além disso, foram feitas buscas manuais nas referências de artigos incluídos. Como critério de elegibilidade foram considerados artigos de relato de caso ou série de casos de MOF publicados na língua inglesa e que apresentassem informações clínicas e histopatológicas suficientes para o diagnóstico de MOF. Foram excluídos artigos que eram cartas ao editor, anais de congressos e artigos de revisão. Quarenta estudos, totalizando 111 casos de MOF foram identificados na literatura. Os casos foram apresentados em 12 países diferentes, sendo a maioria no Brasil (n=41). A média de idade dos indivíduos afetados foi 40.36 ±17.83 anos e a lesão acometeu mais mulheres (n=78/70.27%) na 4ª década de vida. O local anatômico mais afetado foi a gengiva (n=57/52.29%) com características clínicas de nódulo (n=84/100.00%) assintomático (n=76/88.37%). Os exames radiográficos mostraram que na maioria dos casos a lesão não afetou osso (n=16/72.73%). Fibroma (n=53/58.24%) foi a hipótese diagnóstica mais sugerida nos artigos incluídos e o tratamento de escolha foi a remoção cirúrgica (n=93/93.94%). Histologicamente, as lesões foram descritas como bem demarcadas, mas não encapsuladas, contendo um estroma fibromixomatoso frouxo composto por fibroblastos estrelados e fusiformes. O diagnóstico final das lesões de MOF necessitam de análise histopatológico, sendo assim, pode ocorrer o subdiagnóstico. A lesão deve ser incluída como diagnóstico diferencial das lesões benignas de tecidos moles da cavidade oral.

Palavras-chave: Boca, patologia oral, revisão sistemática, mucinose oral focal.

ABSTRACT

Oral focal mucinosis (OFM) is a benign lesion that affects the oral cavity. The exact etiology of this lesion remains unknown. OFM is a rare lesion that was described for the first time in the literature in 1974 by Dr. Tomich and colleagues, who considered it a counterpart of cutaneous focal mucinosis. Given that there are only a few reports in the literature, a review of these cases would be important to summarize the current knowledge about this lesion. The aim of this study was to integrate the demographic, clinical and histopathological characteristics of previously published cases of OFM in a systematic review. The review was registered in PROSPERO. Electronic searches without a publication date restriction were carried out in Embase (Elsevier), PubMed/MEDLINE (National Library of Medicine), Science (Thomson) and Scopus (Elsevier). Furthermore, manual searches were made in the references of included articles. Eligibility criteria were case reports or series of cases of OFM published in english with enough clinical and histopathological information for the diagnosis of OFM. Articles that were letters to the editor, conference proceedings and review articles were excluded. Forty studies reporting 111 cases of OFM were identified in the literature. The cases were reported in 12 different countries, most of them in Brazil (n=41). The mean age of affected individuals was 40.36 ±17.83 years and the lesion was more prevalent in women (n=78/70.27%) in the 4th decade of life. The most affected anatomical site was the gingiva (n=57/52.29%), and the most common presentation was an asymptomatic (n=76/88.37%) nodule (n=84/100.00%). The imagological exams showed that in most cases the lesion didn't affect the bone (n=16/72.73%). Fibroma (n=53/58.24%) was the most common diagnostic hypotheses in the included articles and the usual treatment was surgical removal (n=93/93.94%). Histologically, the lesions were described as well-demarcated but not encapsulated, containing a loose fibro-myxomatous stroma composed of stellate and spindle-shaped fibroblasts. The definitive diagnosis of OFM lesions requires histopathological analysis, and therefore underdiagnosis may occur. The lesion should be included as a differential diagnosis of benign soft tissue lesions of the oral cavity.

Keywords: Mouth, Oral Pathology, Systematic Review, Oral Focal Mucinosis.

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LISTA DE ABREVIATURAS E SIGLAS

ABHYAL	Alcian blue associated with hyaluronidase pre-digestion
AH	Ácido Hialurônico
CAPES	Coordination for the Improvement of Higher Education Personnel
CNPq	Brazilian National Council for Scientific and Technological Development
IHC	Immunohistochemistry
MOF	Mucinose oral focal
N/A	Not available
OFM	Oral focal mucinosis
PAS	Periodic acid-Schiff
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
PROSPERO	International Prospective Register of Systematic Review
UK	United Kingdom

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1 INTRODUÇÃO

A mucinose oral focal (MOF) é uma lesão rara, que envolve os tecidos moles da cavidade bucal, classificada como um tumor benigno de tecido mole (TOBOUTI P. L. et al., 2018; HIGUCHI Y. et al., 2019; CAMERON A. et al., 2020). A MOF foi descrita pela primeira vez em 1974 pelo Dr. Tomich (1974) com base nas características clínicas e histopatológicas de oito casos (TOMICH C. E., 1974). Atualmente, Cunha e colaboradores (2021) em sua revisão de literatura encontraram 100 casos de MOF (CUNHA J. L. S. et al., 2021)

A MOF é retratada como contraparte da mucinose cutânea focal (TOBOUTI P. L. et al., 2018; HIGUCHI Y. et al., 2019). A mucinose cutânea focal foi descrita pela primeira vez em 1966, por Johnson e Helwing (COHEN P. R. et al., 2020; TOMICH C. E., 1974), caracterizada pelo aumento da deposição de mucina na pele (COHEN P. R. et al., 2020; GUTIERREZ N. et al., 2021), devido ao acréscimo na produção de ácido hialurônico (AH) pelos fibroblastos e formação de colágeno (JOHNSON W. C., HELWIG E. B., 1966). Em pacientes com quadros de mucinose focal cutânea múltipla, as doenças sistêmicas podem estar presentes, como síndromes, desordens da tireóide, lúpus eritematoso e doenças autoimunes (GUTIERREZ N. et al., 2021; ALEIXO R. B., 2011), sendo indicado a solicitação de exames laboratoriais (GUTIERREZ N. et al., 2021). No entanto, a mucinose cutânea focal não parece estar associada com quadros sistêmicos, desse modo, não tornando-se necessária a solicitação de exames laboratoriais (GUTIERREZ N. et al., 2021).

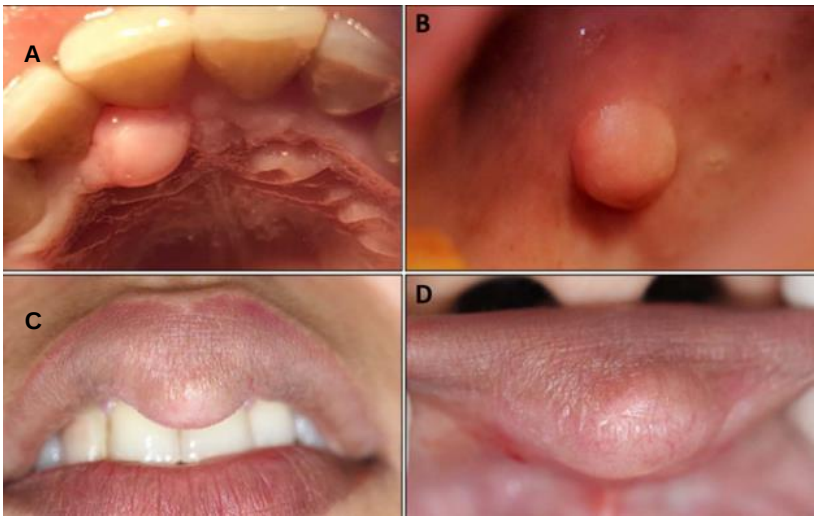
A etiologia exata da MOF permanece desconhecida, embora tenha sido sugerido que o acúmulo de AH produzido por fibroblastos possa causar essa lesão (CUNHA J. L. S. et al., 2021). O AH é um glicosaminoglicano muito presente na matriz extracelular dos tecidos conjuntivos, epiteliais e neurais (NILESH K. et al., 2017). Além disso, sua matriz extracelular é abundante nos tecidos periodontais (SUKUMAR S., DRÍZHAL I., 2007). O AH tem papel importante na lubrificação do tecido conjuntivo muscular, proliferação celular e no reparo de feridas, desempenhando essas funções na cartilagem articular e na pele, respectivamente. Ainda o AH contribui para o aumento de alguns tumores, devido sua participação na propagação e migração celular (VASVANI S. et al., 2020). Dessa maneira, usa-se o AH como marcador tumoral para cânceres de próstata e mama (NILESH K. et al., 2017).

Os fatores patogêncios da MOF continuam muito controversos na litaratura, enquanto alguns autores acreditam que o trauma local possa causar a lesão (BUCHNER A. et al., 1990; CUNHA J. L. S. et al., 2021), Tomich (1974), acredita que a etiologia de MOF não poderia ser por trauma (TOMICH C. E., 1974). Na literatura atual, há estudos que sugerem que o trauma

pode ser o resultado do aumento da produção de AH e mucina, pelos fibroblastos (IEZZI G. et al., 2001; GNEPP D. R. et al., 1990; TIWANA F. et al., 2016; CUNHA J. L. S. et al., 2021). Alguns autores ainda relatam que a MOF pode estar associada com reabsorção radiculares externa (GABAY E. et al., 2010) e reabsorção ósseas (HIGUCHI Y. et al., 2019).

A MOF é mais frequente no sexo feminino entre a quarta e a quinta décadas de vida (TOBOUTI P. L. et al., 2018). Em geral, essa lesão pode acometer qualquer região da cavidade bucal, principalmente a gengiva e o palato como nódulo assintomático (TOBOUTI P. L. et al., 2018; CUNHA J. L. S. et al., 2021) com crescimento submucoso (BARROS FILHO D. C. et al., 2021) e raramente ulcerada (ALEIXO R. B., 2011), como representado na Figura 1. A MOF não apresenta propriedades clínicas ou radiográficas característicos que possibilitem um diagnóstico com base clínica (TOMICH C. E., 1974; CAMERON A. et al., 2020; BARROS FILHO D. C. et al., 2021). Dessa forma, o exame histopatológico é fundamental para o diagnóstico dessa lesão (CAMERON A. et al., 2020; NILESH K. et al., 2017). Devido essa dificuldade no diagnóstico, a MOF muitas vezes é confundida com outras lesões, sendo o Fibroma a hipótese diagnóstica mais comum (ALEIXO R. B., 2011; CUNHA J. L. S. et al., 2021). Em relação ao tratamento, a literatura sugere a completa remoção da MOF (HIGUCHI Y. et al., 2019), seu prognóstico é bom e na maioria das vezes não apresenta recidivas (GONZAGA A. K. et al., 2018).

Figura 1 - Características clínicas da MOF

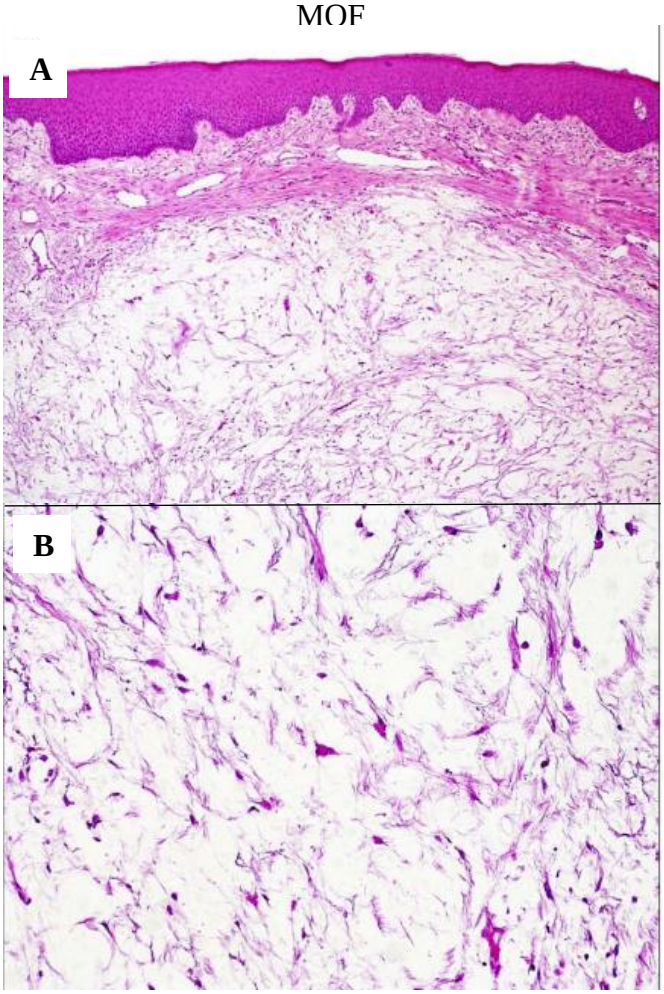


Fonte: Cunha J.L.S. et al., 2021

Legenda figura 1. A) MOF localizada no palato, com coloração semelhante á mucosa. B) Lesão de MOF na região de palato duro. C e D) lesão localizada no lábio superior.

A histopatologia da MOF é caracterizada pela presença de fibras colágenas em um estroma mixóide (GONZAGA A. K. et al., 2018), ocorrendo proliferação dos fibroblastos e aumento na produção de AH, substituindo o tecido conjuntivo, assim, o AH acumula-se entre as fibras colágenas, criando pequenos espaços císticos (TOMICH C. E., 1974; ALEIXO R. B., 2011); em casos raros, a infiltração de células inflamatórias pode estar associada (GONZAGA A. K. et al., 2018). Hitologicamente difere-se de outros tumores benignos de tecido mole por não apresentar um encapsulamento claro, contendo uma área bem demarcada e cercado de tecido colagenoso normal (HIGUCHI Y. et al., 2019). Conforme ilustrado na figura 2, em (A) temos uma área bem demarcada mixomatosa circundada por tecido conjuntivo denso e em (B) uma área mixóide com fibrilas de colágeno separadas por material mucinoso. Além disso, marcadores imuno-histoquímicos como o S100 podem auxiliar no diagnóstico de MOF, sendo o resultado negativo para este anticorpo auxilia na exclusão de alguns diagnósticos diferenciais, como as lesões neurais (ALDRED M. J. et al., 2003; GONZAGA A. K. et al., 2018). O marcador Alcian Blue, positivo nas lesões de MOF, confirma a presença de material mucinoso, também pode ser um recurso para auxiliar no diagnóstico (ALDRED M. J. et al., 2003; GONZAGA A. K. et al., 2018).

Figura 2 – Lâminas histológicas de uma lesão de MOF



Fonte: Cunha J. L. S. et al., 2018

Leganda Figura 2. Coloração de hematoxilina e eosina.

A falta de conhecimento sobre a MOF, semelhança das características clínicas com outras lesões de tecido mole, necessidade de exames histopatológicos e o desconhecimento das suas características histopatológicas para seu diagnóstico, levam a um subdiagnóstico dessa lesão (CUNHA J. L. S. et al., 2020; ALEIXO R. B., 2011). Uma revisão sistemática é importante para fazer uma busca com toda literatura publicada sobre MOF, e com isso, analisar a etiologia, fatores de risco e tratamento. Considerando os poucos relatos na literatura, uma revisão resumindo esses casos seria importante para elucidar a MOF.

2 ARTIGO CIENTÍFICO

Oral focal mucinosis: a systematic review

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ABSTRACT

Introduction: Oral focal mucinosis (OFM) is a rare lesion, described in 1974, but the etiology remains unknown. Clinically OFM presented as an asymptomatic nodular lesion and the similarity of clinical features with other soft tissue injuries makes the diagnosis more difficult. OFM affects more females between the ages of 30 – 49 years.

Objective: The aim of this study was to integrate the demographic, clinical and histopathological characteristics from previously published cases of OFM into a systematic review.

Material and Methods: Electronic searches without publication date restriction were performed in the subsequent databases: Embase, PubMed, Medline, Web of Science, and Scopus. Case reports or case series of OFM published in English and presenting enough clinical and histopathological information were included.

Results: This systematic review identified 40 studies from 12 countries, comprising 111 cases of OFM. This lesion affected more women in the 4th decade of life. The gingiva was the most common anatomical location, followed by the palate. Clinical presentation was an asymptomatic nodule. Imaginological exams revealed that most cases did not have bone involvement. Surgical removal was the treatment of choice for most cases and only one recurrent case was reported.

Conclusions: OFM is an uncommon pathology, and its diagnosis depends on histopathological analysis. The lesion should be included as a differential diagnosis of benign soft tissue lesions of the oral cavity, especially those affecting the gingiva.

Key words: Mouth, Oral Pathology, Systematic Review, Oral Focal Mucinosis.

1. Introduction

Oral focal mucinosis (OFM) is a rare lesion described as a counterpart of cutaneous focal mucinosis (TOBOUTI et al., 2018; HIGUCHI et al., 2019). OFM was first described in 1974 by Dr. Tomich and colleagues based on the clinical and histopathological characteristics of eight cases (TOMICH, 1974). The exact etiology of this lesion remains unknown, although some authors believe that the local trauma may be related to the accumulation of hyaluronic acid produced by fibroblasts (BUCHNER et al., 1990; CUNHA et al., 2021).

OFM is more frequent among females between their fourth and the fifth decades of life (TOBOUTI et al., 2018). In general, this lesion mainly affects the gums and palate as an asymptomatic nodule (TOBOUTI et al., 2018; CUNHA et al., 2021). Histopathologically, OFM is characterized by the presence of collagen fibers embedded in a myxoid stroma; in rare cases, infiltration of inflammatory cells may be associated (GONZAGA et al., 2018). Immunohistochemical markers such as S100 can help with the diagnosis of OFM, with negativity for this antibody being of help to exclude some differential diagnoses such as neural lesions. Alcian blue can also be valuable to differential OFM to odontogenic myxoma (ALDRED et al., 2003; GONZAGA et al., 2018; GABAY E. et al., 2010).

Considering the few reports in the literature, a review summarizing these cases would be important to elucidate OFM. In this sense, the objective of the present systematic review was to integrate the available data published in the literature on OFM in order to obtain the clinical and demographic features of individuals with this condition.

2. Material and Methods

2.1 Information sources and search strategy

Electronic searches without publication date restriction were undertaken in October 2020, and updated in June 2022, in the following databases: Embase (Elsevier), PubMed/MEDLINE (National Library of Medicine), Web of Science (Thomson Reuters), and Scopus (Elsevier). The following search strategy was used for all databases: (mucinoses OR mucinosis OR “oral focal mucinoses” OR “oral focal mucinosis”) AND ("mouth" OR "oral cavity" OR "cavitas oris" OR "oral cavity proper" OR "mouth cavity proper" OR "cavitas oris propria"). The retrieved references were exported to the EndNote software (Thompson Reuters, New York, NY, USA). Duplicates were removed upon identification. Hand searches were also conducted by cross-checking the reference lists of the included articles in order to identify publications that might have been missed during the searches in the electronic databases.

2.2 Eligibility criteria

Articles describing case reports or case series of OFM published in English with enough clinical and histopathological information to confirm the diagnosis were included. Exclusion criteria were letters to the editor, conference proceedings and review articles.

2.3 Study selection and data extraction

Titles/abstracts of all references retrieved through the electronic searches were read by two authors (L.D.F. and L.B.K.). If the title/abstract met the eligibility criteria, the article was included for full text reading. The full text of the articles with titles/abstracts providing insufficient information for a clear decision was also obtained. Following the full text assessment, the references that met the eligibility criteria were included. Disagreements between the two authors were solved upon discussion with a third one (L.F.S.).

For each study included, the following data were extracted by two authors (L.D.F. and L.B.K.) on a standard form: (1) publication details (author, year, and country); (2) patients' sex; (3) age; (4) symptoms; (5) anatomical location of the OFM lesion; (6) clinical presentation; (7) size of the lesion; (8) duration of the lesion; (9) radiological features; (10) diagnostic hypothesis; (11) histopathological features; (12) immunohistochemistry (IHC); (13) special staining; (14) management; (15) presence of recurrence; and (16) follow-up period (months). Unavailable data were defined as not available (N/A.).

2.4 Study certainty assessment

Critical appraisal of the included articles was carried out by means of the Joanna Briggs Institute - University of Adelaide tool for case reports or case series. The included articles were evaluated according to the following parameters: clear description of patient's demographic characteristics, medical history, current clinical condition, clear description of the propaedeutic, treatment, post-intervention clinical condition, adverse events, and lessons provided by the case report, i.e., histopathological analysis with representative description or images. For each parameter, the included article was rated as "yes", "no", "unclear" or "not applicable".

2.5 Other information

This systematic review of case reports of OFM was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement (PAGE M. J. et al., 2020). A protocol was drafted, and registration was carried out at the International Prospective Register of Systematic Reviews (PROSPERO) under the number CRD42020215874.

3. Results

3.1 Study selection

The search strategy through the four electronic databases yielded 417 references. After removal of 95 duplicates, 322 titles and abstracts were assessed according to the inclusion and exclusion criteria. Thirty-three studies were selected for full text evaluation. Seven of these were excluded for the following reasons: full text unavailable, conference abstract, letter to the editor, and language restriction. Fourteen articles were identified by means of the manual search. Therefore, 40 articles reporting 111 cases of OFM were included in the study. In almost all reported cases the patient has a single lesion (only one article described a bilateral palatal lesion). A flowchart depicts the search and selection process **(Figure 1)**.

3.2 Demographic and clinical features

Table I describes the summarized clinical information collected about the cases of OFM identified in this systematic review. The detailed extraction of each study is demonstrated in **Supplementary Table 1**. The cases were reported in the following 12 countries: Brazil (n=41), United States (n=26), Australia (n=16), India (n=12), Japan (n=5), Italy (n=4), Iran (n=2), Canada, Israel, South Korea, Sweden and United Kingdom (UK) (n=1).

Of the 111 patients, females (n=78/70.27%) were more affected with OFM than males (n=33/29.73%), with a female-to-male ratio of 2.36:1. The mean age of the individuals was 40.36 ±17.83 years (range: 2 to 88 years), and the 3rd and 4th decades of life were more prevalent. The mean age of the affected males (47.03 years) was slightly higher than that of the female patients (37.55 years). Regarding the anatomical location, most of the cases affected the gingiva (n=57/52.29%), followed by palate (n=19/17.43%), alveolar ridge (n=12/11.01%), tongue (n=9/8.26%), buccal mucosa (n=4/3.67%), retromolar region (n=4/3.67%), lip

(n=3/2.75%), and floor of the mouth (n=1/0.92%). In two cases, the anatomical location was not precisely informed by the authors. Eighty-four articles described the clinical features of the lesions. OFM was usually a solitary asymptomatic (n=76/88.37%) nodule (n=84/100.00%). Tooth displacement occurred in four cases. The mean size of the lesions was 1.31 cm (range: 0.1 to 10 cm). Sixty-eight reports provided the time of evolution of the lesion, which ranged from 1 month to 10 years and the mean time was 18.10 months.

Twenty-two reports described data about imagological exams. Most of these cases did not show bone involvement associated with the lesion (n=16/72.73%), while six cases showed bone involvement (27.27%) characterized by bone resorption. The most common diagnostic hypotheses were of benign or reactive mesenchymal lesions such as fibromas (n=53/58.24%), pyogenic granulomas (n=13/14.29%), peripheral ossifying fibromas (n=11/12.09%), and peripheral giant cell granulomas/fibromas (n=13/14.29%). In one case (1.10%), the authors suspected a malignant lesion (lymphoma).

Figure 1. Flowchart

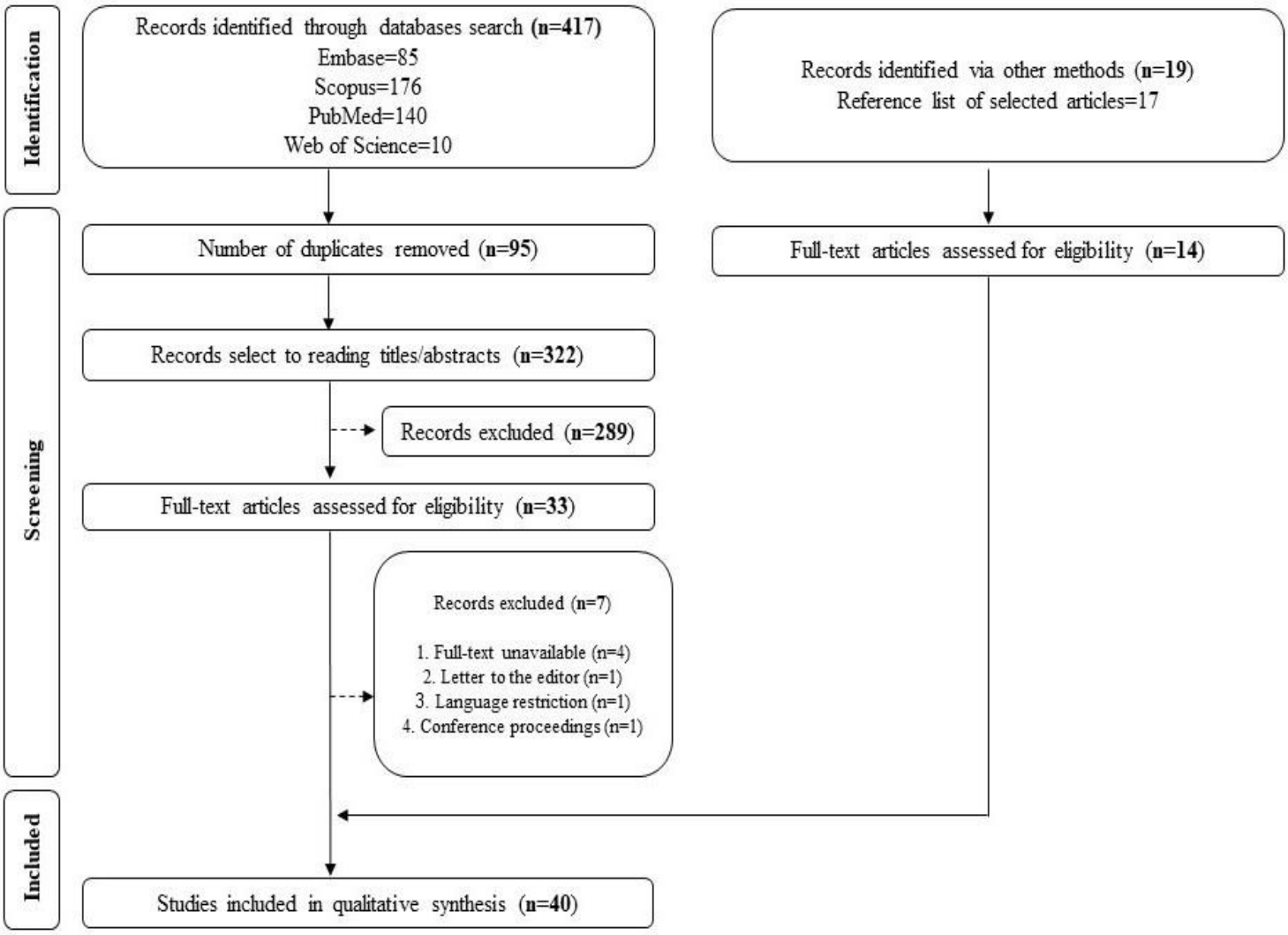

Table I. Demographic and clinical characteristics of the OFM sample

Variable	n (%)
Countries	
Brazil	41 (36.94)
United States	26 (23.42)
Australia	16 (14.41)
India	12 (10.81)
Japan	5 (4.50)
Italy	4 (3.60)
Iran	2 (1.80)
Canada, Israel, South Korea, Sweden and UK	1 (0.90)
Sex (n=111)	
Female	78 (70.27)
Male	33 (29.73)
Age, in years (n=108)	
Mean (SD)	40.36(17.83)
Range	2 – 88
Anatomical location (n=109)	
Gingiva	57 (52.29)
Palate *	19 (17.43)
Alveolar ridge	12 (11.01)
Tongue	9 (8.26)
Buccal mucosa	4 (3.67)
Retromolar region	4 (3.67)
Lip	3 (2.75)
Floor of the mouth	1 (0.92)
Clinical presentation (n=84)	
Nodule	84 (100.00)
Symptoms (n=86)	
No	76 (88.37)
Yes	10 (11.63)
Lesion size (n=81)	
Mean (SD)	1.31 (1,35) cm
Range	0.1–10cm
Evolution time of the lesion, in months (n=68)	
Mean (SD)	18.10 (24.37)
Range	1 – 120
Imaginological exam (n=22)	
Bone resorption	6 (27.27)

No bone involvement	16 (72.73)
Clinical hypothesis (n=91) **	
Fibroma	53 (58.24)
Pyogenic granuloma	13 (14.29)
Peripheral ossifying fibroma	11(12.09)
Peripheral giant cell granuloma	8 (8.79)
Peripheral giant cell fibroma	5 (5.49)
Lymphoma	1 (1.10)
Management (n=99)	
Surgical excision	93 (93.94)
Incisional Biopsy	6 (6.06)
Follow up, in months (n=42)	
Mean (SD)	21.10 (38.71)
Range	0.25–228
Recurrence (n=64)	
No	63 (98.44)
Yes	1 (1.56)

* One case presented bilateral lesions
** Some cases presented more than one clinical hypothesis

3.3 Histopathology, immunohistochemistry and special staining features

Table II presents the description of the histopathological features of each study included in the systematic review. In general, OFM lesions were well-demarcated but not encapsulated, containing a loose fibro-myxomatous stroma composed of stellate- and spindle-shaped fibroblasts. Some reports described the presence of a chronic inflammatory infiltrate and small blood vessels. The main microscopic differential diagnoses were soft tissue myxoma, nerve sheath myxoma, neurofibroma with mucosal degeneration, fibrous hyperplasia, mucocele, and focal myxedema. The immunohistochemical markers and special staining most frequently reported in the studies were anti-S100 (negative in 59 of 61 cases), followed by anti-CD34 (negative in 21 of 21 cases) and anti-α-SMA (negative in 21 of 21 cases). Special staining

techniques used were alcian blue (positive in 66 of 66 cases), Periodic Acid-Schiff (negative in 41 of 43 cases), reticulin staining (negative in 22 of 22 cases) and alcian blue with hyaluronidase pre-digestion (negative in 15 of 15 cases). Thirty-seven cases did not use or report any technique (Supplementary Table 1).

3.4 Treatment, follow-up and recurrence

Surgical removal was the treatment of choice reported in most cases (n=93/93.94%), while an incisional biopsy was performed in six cases (6.06%), with no further treatment mentioned. Ninety-nine publications report data about treatment. Forty-two patients were followed up for a mean time of 21.10±38.71 months after the diagnosis. Of the sixty-four publications that reported data about recurrence, only one showed recurrence (1.5%) on the upper lip after incomplete removal of the lesion **(Table I)**.

Table II. Histopathological features of the OFM cases included in the systematic review

Author, year	Histopathological features
Agha-Hosseini et al., 2018	Hypocellular neoplastic tissue containing numbers star-like elongated cells with hyperchromatic nuclei located in a myxoid matrix
Aldred et al., 2003	Myxomatous tissue with circumscribed region and scattered elongated, stellate and ovoid cells
Atarbashi-Moghadam et al., 2017	Well-circumscribed zone of myxomatous stroma, cells were ovoid, fusiform, or stellate without atypia, surrounded by dense collagenous connective tissue
Bharti et al., 2012	Myxomatous connective tissue stroma, with ovoid, fusiform or stellate-shaped fibroblasts
Bosco et al., 2014	Loose myxomatous connective tissue rich in mucinous material. Fusiform fibroblasts and delicate collagen fibrils
Buchner et al., 1990	Not described
Cameron et al., 2020	Myxoid lesion, well circumscribed and associated with a mild to moderate chronic inflammatory infiltrate at the extremity
Cho et al., 2019	Unencapsulated area of loose, myxomatous connective tissue with short bands of delicate collagen. Stellate and spindle-shaped fibroblasts are scattered throughout the mucinous area
Cunha et al., 2020	Well-circumscribed loose and myxomatous connective tissue. Areas with myxoid appearance composed of loose connective tissue that contained very thin, scattered, and randomly arranged collagen fiber bundles, small blood vessels, and several fibroblasts displaying fusiform, ovoid, and stellate morphology
El Achkar et al., 2016	Well-delimited unencapsulated area of loose myxomatous connective tissue, surrounded by fibrous connective tissue. Fibroblasts were oval, fusiform or star-shaped, interlaced with fibers
	Myxomatous connective tissue area containing star-shaped fibroblasts, surrounded by fibrous connective tissue, well delimited, however, not encapsulated

Ena et al., 2013	Fibro-myxoid stroma, well-localized unencapsulated area of loose tissue, with stellate shaped fibroblasts. Deeper stroma with spindle shaped fibroblasts interspersed between thin collagen fiber bundles and small blood capillaries
Gabay et al., 2010	Well-circumscribed lesion composed of myxomatous connective tissue, which contained numerous stellate-shaped fibroblasts
Garcia et al., 2012	Well-demarcated but not encapsulated area of myxoid tissue with elongated or stellate fibroblasts and small blood vessels
Germano et al., 2008	Myxoid tissue in which fusiform or stellate fibroblasts were immersed
Gnepp et al., 1990	Scattered stellate fibroblasts and small capillaries were included within the mucinous areas
Gonzaga et al., 2018	Well-circumscribed myxoid connective tissue surrounded by a band of dense connective tissue. Myxomatous areas with loose connective tissue and thin, scattered and randomly collagen fiber, several fibroblasts and small-diameter blood vessels
Higuchi et al., 2019	Myxoid matrix with stellate-shaped and spindle-shaped fibroblasts. Fibrous connective tissue
	Myxomatous, stroma with well-delineated borders and few fibers
	Myxomatous stroma with sparsity of fibers
Iezzi et al., 2001	Myxoid connective tissue with spindled and stellate fibroblasts was present
Joshi et al., 2015	Loose myxomatous connective tissue with the deeper stroma composed of star-shaped fibroblasts interspersed between thin bundles of collagen fibers and numerous small capillaries
Ko et al., 2019	Loose fibro-myxoid stroma with fibroblasts – bipolar, fusiform or stellate
Kumar et al., 2015	Myxomatous tissue associated with spindle cells
Lee et al., 2012	Myxomatous connective tissue
Madhusudhan et al., 2010	Loose fibro-myxoid stroma with stellate shaped fibroblasts with the deeper stroma showing spindle shaped fibroblasts interspersed between thin collagen fiber bundles and numerous small blood capillaries

Mattsson et al., 2017	Well-demarcated unencapsulated area with a loosely connected myxomatous connective tissue with slightly enlarged oval fibroblasts
Neto et al., 2014	Areas of loose myxomatous material
Nilesh et al., 2017	Loose and myxomatous connective tissue stroma with scarce inflammatory cells and deeper stroma showing multiple fusiform and stellate-shaped fibroblasts interspersed between thin collagen fiber bundles distributed in the myxomatous background
Pacifici et al., 2012	Fairly well-defined area of myxomatous connective tissue and there were areas of gradual transition from myxomatous connective tissue to surrounding collagenous fibrous connective tissue
Pareek et al., 2019	Keratinized stratified squamous epithelium beneath which loose myxomatous connective tissue stroma was noticed. Sparsely distributed stellate shaped fibroblasts. The underlying connective tissue stroma was minimally inflamed and moderately vascular
Puna et al., 2013	Lamina propria of the oral mucosa with welldefined myxomatous area. Fusiform and stellate fibroblasts with small amount of thin collagen fibers intermingled
Saito et al., 1985	Areas of myxomatous connective tissue surrounded by dense fibrous connective tissue. The myxomatous zone consisted of widely separated collagen fibrils interspersed with stellate fibroblasts, and a slight degree of inflammatory cell infiltration
	Well-localized area of myxomatous connective tissue surrounded by a zone of dense fibrous connective tissue
Silva et al., 2014	Loose myxomatous tissue, surrounded by dense fibrous connective tissue separating them from the epithelial lining. Within the myxomatosis area, an evident proliferation of ovoid, stellate and spindle cells was observed
Lima et al., 2008	Soft tissue mass lined by stratified squamous hyperplastic epithelium with myxomatous connective tissue, interspersed with elongated and stellate fibroblasts
Soda et al., 1998	Area of myxomatous connective tissue with dense but normal collagenous fibrous connective tissue
Sowmya et al., 2015	Loose fibro-myxoid stroma with stellate-shaped fibroblasts

Taufiq et al., 2018	Surface of the lesion was covered by stratified squamous keratinized epithelium overlying the myxoid connective tissue stroma which shows localized region of myxoid material consists of stellate/spindle shaped fibroblasts interspersed between thin delicate collagen fiber and numerous small blood capillaries
Tiwana et al., 2016	Not described
Tomich et al., 1974	Not described
Tobouti et al., 2018	Well-delimited but non-encapsulated lesion, characterized by a myxomatous connective tissue presenting spindle-shaped fibroblasts interspersed with short bundles of collagen
Woo et al., 2014	Subepithelial band of myxoid tissue of low cellularity and the nuclei appeared spindled and bland
Yadav et al., 2016	Well-located areas of loose myxomatous connective tissue stroma surrounded by dense fibrous connective tissue. The myxomatous zone consisted of collagen fibrils and interposed widely spaced stellate-shaped fibroblasts

3.5 Quality assessment

All studies clearly described the diagnostic test methods. Some studies lacked information about demographic characteristics and did not describe correctly the patient's history, current clinical condition or the occurrence of adverse events. However, all case reports provided lessons that could be applied further in case series. Some case series had clear criteria and methods for case inclusion. Several case reports lacked information about the clinical presentation of the patients, but provided a good demographic report. Most publications reported the proposed treatment, but only a few studies followed up the cases. The case reports show a good post-intervention clinical condition **(Supplementary Table 2 and Supplementary Table 3)**.

4. Discussions

The present systematic review confirmed that OFM is an uncommon lesion. From its first description in 1974 to the year 2021, 111 cases of OFM have been described in the English literature. The cases were distributed among 12 different countries, with Brazil being responsible for the greatest number of reported cases. While the etiopathogenesis of OFM is not clearly understood, the lesion is characterized by the local deposition of mucin in connective tissue followed by mucoid degeneration (CAMERON et al., 2020; TIWANA et al., 2016; JOSHI et al., 2015). Tomich and colleagues (1974) stated that trauma does not influence the disordered production of hyaluronic acid by fibroblasts (CUNHA et al., 2021), whereas some authors believe that a traumatic factor can trigger OFM development (TIWANA et al., 2016; NETO et al., 2014; GNEPP et al., 1990). In our systematic review, we found only eight cases in which the OFM lesion could have been associated with trauma. Agha-Hossein and Sadrzadeh-Afshar (2018) believe that hormonal factors are linked to the pathogenesis of OFM (AGHA-HOSSEINI, SADRZADEH-AFSHAR, 2018). They reported a case of OFM occurring in a patient during breastfeeding, with extensive bone resorption at the site of the lesion, which may have been caused by the combined effect of local factors and prolactin with stimulating effects on fibroblasts, resulting in greater production of hyaluronic acid (AGHA-HOSSEINI, SADRZADEH-AFSHAR, 2018).

In the present review, the mean age of the individuals with OFM was 40.36 years, ranging from 2 to 88 years. Recently, Cunha et al. (2020) reported 21 new cases of OFM (CUNHA et al., 2021). They observed a mean age of 48.3 years and confirmed that individuals were more affected in the 4th and 5th decades of life, similar to the results obtained in the present systematic review. A predominance among females (n=78/70.27%) was demonstrated in our study, at a proportion of 2.3:1. Previous studies have shown this predilection for females

and a similar female-to-male ratio (CUNHA et al., 2021; HIGUCHI et al., 2019; ALDRED et al., 2003).

The anatomical location is usually variable. In agreement with the literature, we found that 52.29% of the cases affected the gingiva, followed by the palate (17.43%). Tomich et al. (1974) described lesions anywhere in the oral cavity, but the gingiva was also the most affected site (TOMICH, 1974). Considering this higher prevalence in the gingiva, Cunha et al. (2021) suggested that OFM should be considered a differential diagnosis of nodular lesions occurring at this site (CUNHA et al., 2021). Only one bilateral case of OFM was described, with both lesions affecting the palate of a 2-year-old child (WOO, CHEUNG, 2015). OFM mostly occurs as an extraosseous lesion (HIGUCHI et al., 2019). However, when affecting the jawbones, OFM does not show a preference for the maxilla or mandible. We found just one case of an intraosseous lesion. Interestingly, this review showed that the vast majority of OFM cases affected keratinized mucosa attached to the bone, such as gingiva, palate, alveolar ridge and retromolar area. Taken together, these areas represented more than 80% of cases. On the other hand, only 15.6% of the reported patients were affected in oral soft tissue such as tongue, buccal mucosa, lip or floor of the mouth.

The most reported clinical presentation of OFM was a nodule with firm consistency on palpation, showing a smooth surface and color similar to that of the normal mucosa. Two cases showed an ulceration associated with the lesion that was probably due to chewing (ATARBASHI-MOGHADAM et al., 2017). Tooth displacement is not commonly associated with OFM; however, in this review four cases with this feature were identified probably owing to the large size of the OFM lesion (GONZAGA et al., 2018; SILVA et al., 2014; NILESH et al., 2017). In our results, 76 (88.37%) cases were asymptomatic, in agreement with the literature (CUNHA et al., 2021; GONZAGA et al., 2018). Symptoms related to the OFM lesion (n=10/11.63%) were described as pain exacerbated by cold, touch, speech and difficulty in

speaking and mastication. The clinical differential diagnosis of OFM includes fibroma, pyogenic granuloma, peripheral ossifying fibroma, and peripheral giant cell granuloma. Based on this review, we could confirm that there are no peculiar clinical manifestations or radiographic characteristics that could strongly suggest the diagnostic hypothesis of OFM over these other more common lesions, and that the final diagnosis will depend on histopathological analysis.

The time of OFM evolution varied widely from 1 month to 10 years. Aldred et al. (2003), in their study of 15 cases, found the same variation (ALDRED et al., 2003). In this systematic review, the lesions exhibited a greater size range (0.1 to 10 cm). The largest diameter of the OFM lesion found in this study affected the patient reported by Joshi et al. (2015) – where the lesion had a diameter of 10 cm and localized in gingiva - and with a report of trauma present (JOSHI et al., 2015). Therefore, it could be considered that trauma can aggravate the size of the lesion. OFM lesions do not appear to be associated with any systemic comorbidity, which was also evident in this systematic review. However, Higuchi et al. (2019) believe that it is important to perform blood tests in order to eliminate endocrine diseases that may be related to systemic mucinosis (HIGUCHI et al., 2019).

This condition usually presented as a well-demarcated but not encapsulated lesion, with a loose fibro-myxomatous stroma composed of stellate- and spindle-shaped fibroblasts. Microscopically, the differential diagnosis includes soft tissue myxoma, nerve sheath myxoma, neurofibroma with mucosal degeneration, fibrous hyperplasia, mucocele, odontogenic myxoma, and focal myxedema (CAMERON et al., 2020; GONZAGA et al., 2018; HIGUCHI et al., 2019; DE LIMA et al., 2008; TOMICH, 1974; SAITO et al., 1985). IHC techniques and special stains can be helpful to rule out some soft tissue tumors (GONZAGA et al., 2018). Fifty-three articles included (47.75%) in the present review reported IHC and special staining techniques. The S100 antibody is very important for confirmation of OFM since it allows

differentiating nervous sheath myxoma which is positive for S100 (ALDRED eta al., 2003; CUNHA et al., 2021; GABAY et al., 2010; MADLHUSUDHAN et al., 2010). In this systematic review, we found only two reports of S100-positive cases (3.27%), with the authors believing that the lesion had a possible neural grade or melanocyte differentiation (AGHA-HOSSEINI, SADRZADEH-AFSHAR, 2018). Other important markers used to differentiate OFM lesion from solitary fibrous tumors, myofibroblastic tumors and myxoid appearance are CD34 and α-SMA, respectively – with OFM lesions being negative for all of them (CUNHA et al., 2021). Regarding special staining, positivity for Alcian Blue in all cases in which it was investigated confirmed the presence of mucinous material in the lesion, being compatible with hyaluronic acid. In our study all 22 cases submitted to reticulin staining were negative, indicating the absence of reticular fibers. According to Cunha et al. (2020), OFM lesions may have little or no reticular fibers in myxomatous areas, but may have moderately reticular fibers around blood vessels (CUNHA et al., 2021). All 15 cases of ABHYAL (Alcian blue associated with hyaluronidase pre-digestion) were negative, reinforcing the fact that the presence of hyaluronic acid. Periodic acid-Schiff (PAS) was negative in most cases, confirming the abundance of mucinous material.

The main management of OFM is conservative surgical excision (TOMICH, 1974; ENA et al., 2013; GERMANO et al., 2008; DE LIMA et al., 2008). In this systemic review, only 37.84% of the cases were followed up for periods ranging from 0.25 to 228 months, with only one case demonstrating recurrence.

We acknowledge that this study has some limitations. The major restriction concerns the lack of information reported in the original cases, mainly in case series that lacked clinical information and follow-up. On the other hand, most of the case reports provided demographic characteristics, clear diagnostic test methods, treatment procedure and post-intervention clinical condition. Second, the fact that we only included articles in the English language may not

represent the total number of cases in the literature. However, we trust our data and believe that this restriction does not affect the richness of the findings.

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5. Conclusion

OFM is an uncommon oral pathology clinically characterized as a solitary asymptomatic nodule of firm consistency and mucosa-like color. It affects more women in the fourth decade of life. Its diagnosis must be made through histopathological analysis and its treatment is complete surgical excision. OFM should be included as a differential diagnosis of nodular soft tissue lesions of the oral cavity, especially those that affect keratinized mucosa attached to the bone, particularly in the gingiva.

Supplementary Table 1. Oral Focal Mucinosis identified in the systemic review

Author(s), year of publication	Country	Patient age (years)/sex	Medical history	Anatomical location	Clinical presentation	Reported symptoms and duration	Radiological features	Lesion size (cm)	Diagnostic hypothesis	Special staining	Histopathological features	Treatment	Recurrence	Follow-up period (months)
Agha-Hosseini et al., 2018	Iran	22/F	Breastfeed	Mandibular alveolar ridge	Sessile, pale pink, exophytic with a lobular surface and ulcerated areas at the depth of interlobar fissures	None	Unilocular radiolucent lesion with well-defined irregular borders and involving the left mandibular alveolar ridge	1.5×2.5×3	Central giant cell granuloma	S100: + K-67: + h-caldesmon: - Desmin: - smooth muscle actin: - CDX2: -	Stratified squamous epithelium with some ulcerated areas. The underlying connective tissue was a hypocellular neoplastic tissue containing numbers star-like elongated cells with hyperchromatic nuclei located in a myxoid matrix. Initial histopathological diagnosis was a spindle cell tumor with a myxoid stroma	surgically excised	No	36
Aldred et al., 2003	Australia	38/F	N/A	Lip	Rubbery swelling in labio-buccal soft tissue within upper lip	N/A	N/A	1	N/A	PAS: - Alcian blue: + ABHYAL: - S100: -	Myxomatous tissue with circumscribed region and scattered elongated, stellate and ovoid cells.	surgically excised	No	228
		30/F	N/A	Mandibular Gingiva (1st molar)	Firm, sessile, pink/purple swelling	None 1 month	N/A	0,3	Fibrous epulis	PAS: - Alcian blue: + ABHYAL: - S100: -		surgically excised	No	84
		16/F	N/A	Mandibular Gingiva (Anterior labial)	Firm, pedunculated, swelling left	None 4 months	N/A	0,8 x 0,5	Fibrous hyperplasia	PAS: - Alcian blue: + ABHYAL: - S100: -		surgically excised	No	N/A
		56/F	N/A	Buccal Mucosa	Pedunculated polyp	N/A	N/A	1 x 0,5	N/A	PAS: - Alcian blue: + ABHYAL: - S100: -		surgically excised	No	N/A
		60F	N/A	Mouth	Pedunculated, pink swelling	None >12 months	N/A	0,9 x 0,8 x 0,3	Squamous papilloma	PAS: - Alcian blue: +		surgically excised	No	10

								ABHYAL: - S100: -			
49/M	N/A	Mandibular Gingiva (1st premolar)	Pedunculated swelling	None 120 months	N/A	0,5	Polyp	PAS: - Alcian blue: + ABHYAL: - S100: -	surgically excised	No	None
31/F	N/A	Gingiva	Firm, pink swelling palatal gingiva	None 6 months	N/A	1,5	Giant cell granuloma	PAS: - Alcian blue: + ABHYAL: - S100: -	surgically excised	No	None
52/M	N/A	Mandibular Gingiva (2nd molar)	Firm swelling	None 12 months	N/A	0,7	Fibrous epulis	PAS: - Alcian blue: + ABHYAL: - S100: -	surgically excised	No	None
74/M	N/A	Lip	Lower lip swelling	N/A	N/A	N/A	N/A	PAS: - Alcian blue: + ABHYAL: - S100: -	surgically excised	N/A	N/A
40/F	N/A	Mandibular Gingiva (2nd premolar and 1st molar)	Asymptomatic swelling buccal	None 4 months	N/A	0,8 x 0,5	Fibroma	PAS: - Alcian blue: + ABHYAL: - S100: -	surgically excised	No	1 week
55/M	N/A	Tongue	Firm, pedunculated, grey/white swelling	None 3 months	N/A	0,5	Fibroepithelial polyp	PAS: - Alcian blue: + ABHYAL: - S100: -	surgically excised	No	1
37/F	N/A	Gingiva	Firm, pedunculated polyp on gingiva distal to left mandibular second molar	None 3 months	N/A	Not stated	Not known	PAS: - Alcian blue: + ABHYAL: - S100: -	surgically excised	No	8
35/F	N/A	Mandibular Gingiva crest (2nd molar)	Firm, pedunculated swelling of mucosa	None 12 months	N/A	0,5 x 0,3 x 0,3	Fibrous epulis	PAS: - Alcian blue: + ABHYAL: - S100: - Alcian blue: + ABHYAL: - S100: -	surgically excised	N/A	None

		33/F	N/A	Mandibular Gingiva vestibular (1st molar)	Firm mass gingival margin buccal	None 12 months	N/A	0,6	Fibrous epulis	PAS: - Alcian blue: + ABHYAL: - S100: -		surgically excised	N/A	None
		68/M	N/A	Mandibular Gingiva crest (edentulous – 2nd molar	Firm, pedunculated swelling covered by normal mucosa	None 12 months	N/A	1 x 0,5	Fibroepithelial polyp	PAS: - Alcian blue: + ABHYAL: - S100: -		surgically excised	N/A	1 week
Atarbashi-Moghadam et al., 2017	Iran	49/M	None	palatal gingiva towards the palate	Nodular mass covered by partially ulcerated mucosa, large Pedunculated and firm	None 60 months	N/A	3 x 3	Peripheral Ossifying Fibroma, Peripheral Giant Cell Granuloma and Pyogenic Granuloma	N/A	Nodular mass covered by partially ulcerated mucosa, composed of a well-circumscribed zone of myxomatous stroma (cells were ovoid, fusiform, or stellate without atypia) surrounded by denser - collagenous connective tissue	surgically excised	No	36
Bharti et al., 2012	India	32/F	None	Posterior palatal mucosa	pinkish red, painless, sessile, firm and tender mass	None 4-5 months	No evidence of crestal bone loss, and the lamina dura was intact around the roots of distal of 16 to the mesial of 18	1,5	Fibrous hyperplasia	N/A	Myxomatous connective tissue stroma, with ovoid, fusiform or stellate-shaped fibroblasts.	surgically excised	No	12
Bosco et al., 2014	Brazil	42/M	N/A	Gingiva (maxillary central incisor)	Firm mass and similar mucosa color	Painless 72 months	Not appear to affect the integrity of the periodontal ligament of adjacent teeth	1,5	N/A	Alcian blue +	Loose myxomatous connective tissue (CT) rich in mucinous material. Fusiform fibroblasts and delicate collagen fibrils were also detected	surgically excised	No	144
Buchner et al., 1990	USA	18/F	N/A	Mandibular gingiva (2nd premolar and 1st molar)	N/A	None 9 months	N/A	2	N/A	N/A	N/A	surgically excised	No	N/A

30/M	N/A	Mandibular gingiva (2nd molar)	N/A	None 60 months	N/A	1,6	N/A	N/A	N/A	surgically excised	No	N/A
32/F	N/A	Maxillary gingiva (central and lateral incisors)	N/A	None 1 month	N/A	0,3	N/A	N/A	N/A	surgically excised	No	N/A
22/F	N/A	Maxillary gingiva	N/A	None 12 months	N/A	0,9	N/A	N/A	N/A	surgically excised	No	N/A
53/F	N/A	Mandibular gingiva (2nd molar)	N/A	None N/A	N/A	1	N/A	N/A	N/A	surgically excised	No	N/A
16/F	N/A	Maxillary gingiva	N/A	None N/A	N/A	0,6	N/A	N/A	N/A	surgically excised	No	N/A
43/M	N/A	Mandibular gingiva (1st molar)	N/A	None N/A	N/A	1	N/A	N/A	N/A	surgically excised	No	N/A
61/F	N/A	Mandibular alveolar mucosa (2nd molar)	N/A	None N/A	N/A	0,8	N/A	N/A	N/A	surgically excised	No	N/A

37/F	N/A	Maxillary alveolar mucosa (central incisors)	N/A	None N/A	N/A	0,6	N/A	N/A	N/A	surgically excised	No	N/A
41/F	N/A	Mandibular gingiva (2nd molar)	N/A	None N/A	N/A	0,9	N/A	N/A	N/A	surgically excised	No	N/A
37/F	N/A	Mandibular gingiva (1st molar)	N/A	None 36 months	N/A	1,2	N/A	N/A	N/A	surgically excised	No	N/A
46/M	N/A	Mandibular gingiva	N/A	None 12 months	N/A	0,3	N/A	N/A	N/A	surgically excised	No	N/A
38/F	N/A	Hard palate	N/A	None 12 months	N/A	0,7	N/A	N/A	N/A	surgically excised	No	N/A
46/M	N/A	Mandibular retromolar area	N/A	None 36 months	N/A	3,5	N/A	N/A	N/A	surgically excised	No	N/A
50/M	N/A	Anterior ventral tongue	N/A	None 2 months	N/A	0,4	N/A	N/A	N/A	surgically excised	No	N/A

Cameron et al., 2020	UK	14/F	None	Palate (between 1st and 2nd premolar)	Soft tissue. Overlying mucosa was normal and non-ulcerated	None N/A	Without root resorption or bone loss of the alveolar crest	0,7 x 0,6	Fibroma,pyogenic granuloma, fibrous epulis, giant cellfibroma, gingival hyperplasia, peripheral odontogenic fibroma, fibrous hyperplasia, fibro-epithelial polyp or peripheral giant cell granuloma.	N/A	Covering myxoid lesion has non-dysplasticsquamous epithelium. The lesion is well circumscribed and is associated with amild to moderate chronic inflammatory infiltrate at the extremity. In myxoid stroma there are acute and chronic inflammatory cells	surgically excised	No	At this moment
Cho et al., 2019	USA	13/F	Anxiety, attention deficit hyperactivity disorder and global developmental delay	Mandibular gingiva facial and lingual (1st and 2nd molar)	Pink, sessile, non-ulcerated, multilobulated hyperplastic tissue masses, firm consistency, no fluctuation	None A few weeks	Without osseous lesions around the teeth and intact lamina dura	1,5	Reactive soft tissue from a healingintraoral laceration. Fibroma, peripheral ossifying fibroma, peripheral giant cell granuloma, peripheral odontogenic fibroma	S-100: + Marked a few scattered melanocytes and dendritic cells in the epidermis, but not in the mucinous areas.	Well-localised, unencapsulated area of loose, myxomatous connective tissuewith short bands of delicate collagen.Stellate andspindle-shaped fibroblasts are scattered throughoutthe mucinous area.	First an incisional Biopsy, and then a Excisional biopsy	No	2
Cunha et al., 2021	Brazil	30/F	N/A	Hard palate	Mucosa color, dome-shaped, smooth surface and resilient consistency	None 2 months	N/A	0,5	Gingival hyperplasia and Peripheral ossifying fibroma	Alcian blue: + PAS: - Reticulin stainin: - S100 protein, CD34, or α-SMA: -	Well-circumscribed loose and myxomatous connective tissue surrounded by dense connective tissue of variable thicknessbeneath the epithelium. The areas with myxoid appearance were composed of loose connective tissue that contained very thin, scattered,and randomly arranged collagen fiber bundles, small blood vessels, and several fibroblasts displaying fusiform, ovoid, and stellate morphology.	surgically excised	N/A	N/A
		30/F	N/A	Gingiva	Mucosa color, Dome-shaped, smooth surface and Fibroelastic consistency	None N/A	N/A	N/A	Fibrous hyperplasia			surgically excised	No	6
		57/M	N/A	Buccal mucosa	Yellow, Dome-shaped, smooth surface and soft consistency	None N/A	N/A	0,5	Lipoma and Inflammatory fibrous hyperplasia			surgically excised	N/A	N/A
		8/M	N/A	Gingiva	Mucosa color, Dome-shaped and firm consistency	None 36 months	N/A	3	Pyogenic granuloma			surgically excised	N/A	N/A

77/M	N/A	Buccal mucosa	Bluish, Dome-shaped, smooth surface and soft consistency	None 12 months	N/A	1	Fibrous hyperplasia	surgically excised	N/A	N/A
61/F	N/A	Hard palate	Pink, Dome-shaped, smooth surface and soft consistency	None N/A	N/A	1	Fibrous hyperplasia	surgically excised	N/A	N/A
27/F	N/A	Gingiva	Mucosa color, Dome-shaped, smooth surface and soft consistency	None 24 months	N/A	0,1	Pyogenic granuloma	surgically excised	N/A	N/A
48/F	N/A	Gingiva	Mucosa color, Dome-shaped, smooth surface and soft consistency	None 24 months	N/A	1,5	Pyogenic Granuloma, Peripheral ossifying fibroma and peripheral giant cell fibroma	surgically excised	N/A	N/A
67/F	N/A	Gingiva	Mucosa color, Dome-shaped, smooth surface and soft consistency	None 36 months	N/A	6	Pyogenic granuloma, Peripheral ossifying fibroma and peripheral giant cell fibroma	surgically excised	N/A	N/A
47/F	N/A	Alveolar ridge mucosa	White and dome-shaped	None N/A	N/A	0,9	Peripheral ossifying fibroma and Pyogenic Granuloma	surgically excised	N/A	N/A
63/F	N/A	Tongue	Mucosa color, Dome-shaped, smooth surface and Fibroelastic consistency	None 48 months	N/A	1	Fibrous hyperplasia	surgically excised	N/A	N/A
62/M	N/A	Tongue	Red, Dome-shaped, smooth surface and Fibroelastic consistency	N/A	N/A	0,3	Fibrous hyperplasia	surgically excised	N/A	N/A

74/F	N/A	Retromolar region	Mucosa color, Dome-shaped, smooth surface and Firm consistency	None 8 months	N/A	1,4	Fibrous hyperplasia	surgically excised	N/A	N/A
62/M	N/A	Palate	Mucosa color, nodular, smooth surface and Firm consistency	None N/A	N/A	N/A	N/A	surgically excised	N/A	N/A
28/M	N/A	Floor of the mouth	Red, Lobulated, smooth surface and Firm consistency	Pain 4 months	N/A	N/A	Fibroma	surgically excised	No	36
22/F	N/A	Gingiva	Pink, Dome-shaped, smooth surface and soft consistency	None 7 months	N/A	0,2	Pleomorphic adenoma	surgically excised	N/A	N/A
75/F	N/A	Alveolar ridge mucosa	Mucosa color, nodular, smooth surface and Firm consistency	N/A	N/A	1,6	Fibrous hyperplasia	surgically excised	No	8
64/F	N/A	Alveolar ridge mucosa	Mucosa color, Dome-shaped, smooth surface and Fibroelastic consistency	None N/A	N/A	2	Fibrous hyperplasia	surgically excised	No	12
27/F	N/A	Upper lip	Mucosa color, nodule, smooth surface and soft consistency	Pain 60 months	N/A	1,2	Mucocele	surgically excised	Yes	N/A
35/F	N/A	Hard palate	Mucosa color, Dome-shaped, smooth surface and soft consistency	None N/A	N/A	0,5	Fibroma	surgically excised	N/A	N/A

		N/A /M	N/A	Alveolar ridge mucosa	Mucosa color, Dome-shaped, smooth surface and firm consistency	Pain 6 months	N/A	1	Fibrous hyperplasia			surgically excised	N/A	N/A
El Achkar et al., 2016	Brazil	35/F	N/A	Gingiva (2nd molar)	Mucosa color and texture, nodule with a sessile base, firm on palpation	None A few months	N/A	1	Irritation fibroma, lipoma or peripheral ossifying fibroma	Alcian Blue: +	Mucosa with an well delimited unencapsulated area of loose myxomatous connective tissue in the lamina propria, surrounded by fibrous connective tissue. Fibroblasts were oval, fusiform-or star-shaped, interlaced with fibers. In the adjacent connective tissue, there were blood vessels and inflammatory infiltrates	surgically excised	No	N/A
		35/M	N/A	Alveolar mucosa	White, nodule	None48 months	N/A	0,5	Fibrous hyperplasia and fibroma	Alcian Blue: +	Myxomatous connective tissue area containing star-shaped fibroblasts, surrounded by fibrous connective tissue, well delimited, however, not encapsulated	surgically excised	No	N/A
Ena et al., 2013	India	26/M	Trauma	Gingiva (2nd and 3rd molar)	Reddish, well-demarcated, pedunculated, partly smooth and shiny. Blanching, bleeding, pinpoints and ovoid	None 12 months	N/A	1,5 x 1,5	N/A	N/A	Stratified squamous hyper-parakeratinized epithelium and the connective tissue fibro-myxoid stroma, well-localized unencapsulated area of loose, with stellate shaped fibroblasts. Deeper stroma with spindle shaped fibroblasts interspersed between thin collagen fiber bundles and small blood capillaries.	surgically excised	No	8
		36/F	N/A	Gingiva (central incisors)	Round in shape, firm, sessile and non-tender to palpation. The overlying mucosal surface was	None N/A	N/A	0,8 x 0,7	N/A	N/A	stratified squamous hyper-parakeratinized epithelium and the connective tissue fibro-myxoid stroma with stellate shaped Fibroblasts. Deeper stroma with spindle	surgically excised	No	6

					smooth, not ulcerated and mucosa color						shaped fibroblasts interspersed between thin collagen fiber bundles and small blood capillaries.			
Gabay et al., 2010	Israel	44/F	Good	Mandibular Gingiva (1st molar)	Firm and localized. 1st molar: thermal pain and asymptomatic with percussion test	Pain with cold 36 months	Round radiolucent lesion located on the 1st molar and cervical external root resorption	N/A	Fibrous hyperplasia, peripheral giant cell granuloma, peripheral odontogenic fibroma and peripheral ossifying fibroma, or initial stage organizing epulis granuloma	S-100: - Reticulin: - Alcian blue: +	Well-circumscribed lesion composed of myxomatous connective tissue, which contained numerous stellate-shaped fibroblasts	Incisional biopsy	No	6
Garcia et al., 2012	Brazil	N/A /F	Orthodontic patient (bacterial plaque accumulation, after the placement of the orthodontic tube, associated with the orthodontic movement causing a local inflammatory process in gingiva area)	Gingiva (1st molar)	Reddish, sessile, firm, well-defined nodule	2 months	No alterations neither in the underlying bone or in the adjacent teeth	1 (0,9 × 0,5 × 0,5)	Inflammatory fibrous hyperplasia or peripheral giant cells lesion	Alcian Blue +	Well-demarcated but not encapsulated area of myxoid tissue with elongated or stellate fibroblasts and small blood vessels. The overlying mucosa composed by stratified squamous ephitelium was unremarkable	surgically excised	No	12
Germano et al., 2008	Italy	35/M	Non-contributory	Gingiva (central incisive)	Sessile, with hard consistency, adherent to the underlying tissues and pinkish in colour	N/A	N/A	1	N/A	Pas Alcian +	Myxoid tissue in which fusiform or stellate fibroblasts were immersed	surgically excised	No	6
Gnepp et al., 1990	USA	4/F	Cleft lip and cleft palate. Hydrocephalus, left facial paralysis, bilateral mixed hearingloss, and esophageal dyskinesia	Hard palate	Firm. Biopsy mass were white-gray and the opposite surface was pink.	N/A	N/A	1.5 x 0.8 x 0.5 and 0.8 x 0.5 x 0.5 mean 1,15	N/A	Mucicarmine, colloidal iron, and alcian blue: +	A well-localized submucosal. Didn't contain reticulin fibers. Scattered stellate fibroblastsand small capillaries were included within the mucinous areas, but wasn´t any inflammatoryinfiltrate and cellular lining at the junction of themyxoid tissue with the surrounding collagen.	surgically excised	N/A	N/A

Gonzaga et al., 2018	Brazil	47/F	N/A	Alveolar ridge	Pediculated.	Toothache 6 months	N/A	N/A	Granulation tissue	Alcian blue: + S-100: -	well-circumscribed myxoid connective tissue surrounded by a band of dense connective tissue. Myxomatous areas: loose connective tissue, with thin, scattered and randomly collagen fiber, several fibroblasts (spindle, stellate, and round), and small-diameter blood vessels.	surgically excised	N/A	N/A
		78/M	N/A	Hard palate	Hyperplasic	None N/A	N/A	N/A	Fibroma	Alcian blue: + S-100: -		N/A	N/A	N/A
		60/F	N/A	Alveolar ridge	N/A	N/A 2 months	N/A	N/A	Fibrous hyperplasia	Alcian blue: + S-100: -		surgically excised	N/A	N/A
		39/F	N/A	N/A	Hyperplastic. Sessile	N/A	N/A	N/A	Pyogenic granuloma	Alcian blue: + S-100: -		N/A	N/A	N/A
		33/F	N/A	Gingiva	Pediculated	None 36 months	N/A	N/A	Gingival hyperplasia	Alcian blue: + S-100: -		surgically excised	N/A	N/A
		23/F	N/A	Gingiva	Tumoral aspect. Sessile. Tooth displacement	None 3 months	N/A	N/A	Peripheral Giant Cell Granuloma, Peripheral ossifying fibroma and Fibroma	Alcian blue: + S-100: -		surgically excised	N/A	N/A
		33/F	N/A	Gingiva	Tumoral aspect. Tooth displacement	None N/A	N/A	N/A	N/A	Alcian blue: + S-100: -		surgically excised	N/A	N/A
		63/M	N/A	Alveolar ridge	Nodule and pediculated	None 10 months	N/A	N/A	Peripheral Giant Cell Granuloma	Alcian blue: + S-100: -		surgically excised	N/A	N/A
		27/F	N/A	Gingiva	Sessile and fibrous	N/A 6 months	N/A	N/A	Fibroma	Alcian blue: + S-100: -		surgically excised	N/A	N/A
		37/F	N/A	Hard palate	Papillomatous. Pediculated	None N/A	N/A	N/A	Papilloma	Alcian blue: + S-100: -		N/A	N/A	N/A
		43/F	N/A	Hard palate	Sessile and Soft consistence	None N/A	N/A	N/A	Pleomorphic adenoma	Alcian blue: + S-100: -		Incisional biopsy	N/A	N/A
Higuchi et al., 2019	Japan	26/M	N/A	Retromolar region	Normal color and no swelling	N/A	Panoramic Radiographic and Computed Tomography: well-demarcated radiolucent/ low-density area	1,7 x 1,2	Tumor	Alcian blue: + PAS: - S-100: - Silver staining: + (Sparse)	Myxoid matrix: stellate-shapedand spindle-shaped fibroblasts.Fibrous connective tissue.There was no clear encapsulation of the tissue mass	surgically excised	No	24

		60/F	N/A	Gingiva (canine and 1st premolar)	Swelling	None 9 months	without bone resorption	0,7 x 0,6	Epulis of the gingiva	Alcian blue: + PAS: - S-100: - Silver staining: -	Myxomatous, stroma with well-delineated borders and few fibers	surgically excised	No	24
		47/F	N/A	Gingiva (canine and 1st premolar)	The mass was partial redness and non-pedunculated. Elastic hardness and no mobility in gingiva	None 13 months	Without bone resorption	1 x 1	Epulis of the gingiva	Alcian blue: + PAS: - S-100: - Silver staining: -	Myxomatous stroma: sparsity of fibers. Mild infiltration of plasma cells around the periphery of the blood vessels	surgically excised	No	12
Iezzi et al., 2001	Italy	48/M	Non-contributory	Mandibular gingiva (central incisor)	Firm, redness and swelling	Tender to the touch 8 months	Erosion wasn't present on the underlying bone. Amesial intrabony defect of the left mandibular cen-tral incisor was present	1	Periodontal abscess	Alcian blue: +	Myxoid connective tissue with spindledand stellate fibroblasts was present.	First an incisional Biopsy, and then a Excisional biopsy	No	4
Joshi et al., 2015	India	53/F	Healthy. Trauma in OFM	Mandibular Gingiva (canine to 2nd premolar)	Pale pink with flecks of melanin pigmentation, firm, fibrous, sessile. Smooth and non-lobulated surface. Well defined borders	None 7-8 months	Mild horizontal interproximal crestal bone loss between 33 and 34. Vertical interproximal bone loss between 34 and 35. Lamina dura and periodontal ligament were intact	10 x 2	Irritation fibroma	Alcian blue: +	Stratified squamous hyper-parakeratinized epithelium. Loose myxomatous connective tissue. Deeper stroma composed of star-shaped fibroblasts interspersed between thin bundles of collagen fibers and numerous small capillaries	surgically excised	No	3
Ko et al., 2019	South Korea	70/F	Healthy	Tongue base	Well demarcated, without invasion or ulceration and firm	N/A	N/A	1	Benign tumor arising from a minor salivary gland	S-100: -	Loose fibro-myxoid stroma with fibroblasts (bipolar, fusiform or stellate).	surgically excised	No	3 weeks

Kumar et al., 2015	India	25/F	None	Posterior inferior gingiva	Reddish, sessile, firm, well-defined mass	Painless 4 months	No bone involvement	1	Pyogenic granuloma or irrational fibroma	N/A	Myxomatous tissue associated with spindle cells	surgically excised	No	12
Lee et al., 2012	Australia	17/F	Lymphoblastic leukemia. Epilepsy and mild intellectual disability	Gingival papilla lingual	Firm, sessile and non-tender to palpation. The overlying mucosal surface was smooth, not ulcerated and appeared the same colour as the surrounding mucosa.	None Unknown	No changes were noted in the area of the soft tissue lesion	0,6	N/A	Alcian blue: +	Myxomatous connective tissue with a plasma cell infiltrate on haematoxylin and eosin stained sections	surgically excised	No	1 week
Madhusudhan et al., 2010	India	50/M	Chew tobacco in the past (4 years ago)	Hard palate	well-defined, pinkish, sessile	Mild pain during speech. 2 months	N/A	1 x 0,75	Gingival epulis	Vimentin: + S-100: -	Stratified squamous hyper-parakeratinized epithelium and the underlying connective tissue stroma was composed of loose fibro-myxoid stroma with stellate shaped fibroblasts. Deeper stroma showed spindle shaped fibroblasts interspersed between thin collagen fiber bundles and numerous small blood capillaries.	surgically excised	No	8
		26/F	N/A	Gingiva (1st molar)	Firm, nontender and sessile. The cut surface of the excised specimen showed a transparent, jelly like mucinous substance	Difficulty in speaking and mastication. 3 months	N/A	1,2	Fibrous epulis of the gingiva			surgically excised	No	8
Mattsson et al., 2017	Sweden	88/F	Thyroiditis, hypertension, bradycardia, angina pectoris and pain from the neck	Tongue	Surface was smooth and no inflammatory reaction could be seen in the adjacent tissue. Solid on palpation and appeared to extend down to the underlying muscle	N/A	N/A	1	Focal epithelial hyperplasia	EMA: - S-100: -	Relatively well demarcated area with a loosely connected myxomatous connective tissue with slightly enlarged oval fibroblasts. The lesion was lobulated, and circumscribed, but unencapsulated. The squamous epithelium was without significant alteration.	surgically excised	N/A	N/A

Neto et al., 2014	Brazil	20/F	Healthy. Might be associated with surgically assisted rapid maxillary expansion	Attached gingiva (maxillary central incisors)	Firm, sessile and same color as the mucosa, although a slight erythematous area was noted. The overlying mucosa was not ulcerated.	None	No changes were noted	1	N/A	Alcian blue: +	Fragments of mucosa that were partially covered with hyperparakeratinized stratified squamous epithelium with the areas of acanthosis. The lamina propria consisted of dense connective tissue permeated by an intense, diffuse mononuclear inflammatory infiltrate. Throughout the connective tissue, there were areas of loose myxomatous material	surgically excised	No	24
Nilesh et al., 2017	India	58/F	Healthy	palate	Firm swelling with the molar teeth were displaced, mobile and appeared partially submerged in the mucosa	Painless 6 months	Resorption of the left posterior maxillary alveolus with floating maxillary molars	4.5	Peripheral giant cell lesion, peripheral ossifying fibroma, pyogenic granuloma, traumatic fibroma and focal gingival hyperplasia	Alcian blue showed strong staining suggestive of hyaluronic acid. S100: -	Loose and myxomatous connective tissue stroma with scarce inflammatory cells underlying the epithelial lining. Deeper stroma showed multiple fusiform and stellate-shaped fibroblasts interspersed between thin collagen fiber bundles distributed in the myxomatous background	surgically excised	No	12
Pacifici et al., 2012	Italy	62/F	N/A	Tongue	Small, solid and round-shaped neoformation	Painless	N/A	0.5	N/A	S100 and desmin: - Vimentin: + Alcian Blue: +	Fairly well-definedarea of myxomatous connective tissue. Theborders were partially delimited and therewere areas of gradual transition from myxomatousconnective tissue to surrounding collagenousfibrous connective tissue	surgically excised	N/A	N/A
Pareek et al., 2019	India	22/F	N/A	Gingiva	Pedunculated gingival swelling	Painless 12 months	N/A	1 x 1	Fibroma and Fibroepithelial polyp	N/A	keratinized stratified squamous epithelium beneath which loose myxomatous connective tissue stroma was noticed. Sparsely distributed stellate shaped fibroblasts. The underlying connective tissue stroma was minimally	surgically excised	N/A	N/A

											inflamed and moderately vascular			
Puna et al., 2013	Brazil	30/F	None	Palate	Sporadic bleeding in small quantities. Nodular, fibroelastic consistency, pale pink, pedicled and without ulcerated areas	Pain	N/A	1	N/A	N/A	Lamina propria of the oral mucosa with welldefined myxomatous area. Fusiform and stellate fibroblasts with small amount of collagen fibers intermingled.	surgically excised	No	12
Saito et al., 1985	Japan	35/M	N/A	Anterior inferior gingiva	Well-demarcated mass, same collor of the mucosa	Painless	No bone involvement	N/A	Fibroma	N/A	Areas of myxomatous connective tissue surrounded by dense fibrous connective tissue. The myxomatous zone consisted of widely separated collagen fibrils interspersed with stellate fibroblasts, and a slight degree of inflammatory cell infiltration	surgically excised	N/A	N/A
		50/F	N/A	Anterior inferior gingiva	Sweeling	N/A	No bone involvement	N/A	Fibroma	N/A	Well-localized area ofmyxomatous connective tissue surrounded by a zone ofdense fibrous connective tissue	surgically excised	N/A	N/A
Silva et al., 2014	Brazil	23/F	N/A	Gingiva (causing displacement of the right first molar)	sessile, firm, and the overlying mucosa was non-ulcerated and presented no colour alterations	N/A	N/A	N/A	Peripheral giant cell lesion, peripheral ossifying fibroma and traumatic fibroma	Alcian blue + Periodic acid-Schiff (PAS) + S-100 -	Subepithelial area, circumscribed masses of loose myxomatous tissue were observed, surrounded by dense fibrous connective tissue separating them from the epithelial lining. Within the myxomatosis area, an evident proliferation of ovoid, stellate and spindle cells was observed.	Surgically excised	No	36

Soares de Lima et al., 2008	Brazil	36/F	None	Gingiva (maxillary left canine)	Sweeling, reddish, sessile, firm, tender, well-demarcated mass	Painless 4 months	No bone alteration	1	Gingival hyperplasia, pyogenic granuloma, or fibroma	PAS: - Toluidine blue: + Alcian blue: +	Soft tissue mass lined by stratified squamous hyperplastic epithelium with myxomatous connective tissue, interspersed with elongated and stellate fibroblasts	Surgically excised	No	24
Soda et al., 1998	Italy	68/M	N/A	Tongue	Whitish soft swelling	None 36 months	N/A	N/A	N/A	Alcian Blue: + Vimentin: + S100 and desmin: - PAS: -	Area of myxomatous connective tissue. The border zone was only partially well delineated and there were areas of gradual transition from the myxomatous tissue to the surrounding relatively dense but normal collagenous fibrous connective tissue.	surgically excised	N/A	N/A
Sowmya et al., 2015	India	54/M	None	Right posterior gingiva	Well-defined, pinkish, pedunculated, roughly ovoid shaped growth	Pain 3 months	N/A	2x1.5	Fibrous epulis	Vimentin + S100 -	Stratified squamoushyper-parakeratinised epithelium and the underlying connective tissue stroma was composed of loose fibromyxoid stroma with stellate-shaped fibroblasts	surgically excised	No	12
Taufiq et al., 2018	India	15/F	Healthy	Retromolar region	Firm and fibrous gingival overgrowth and oval shape. Well demarcated, pedunculated, smooth and had well defined borders, pale pink color	Painless 6 months	N/A	1.5 × 1.5	Fibroma	N/A	surface of the lesion was covered by stratified squamous keratinised epithelium overlying the myxoid connective tissue stroma which shows localized region of myxoid material consists of stellate/spindle shaped fibroblasts interspersed between thin delicate collagen fiber and numerous small blood capillaries	Surgically excised	No	6
Tiwana et al., 2016	USA	29/F	Developed marginal gingival inflammation subsequent to aesthetic crown lengthening surgery	gingival margin	Well-demarcated erythematous gingival lesion close to the free gingival	N/A	N/A	N/A	Allergic reaction to methacrylate, candida infection, foreign body gingivitis and	N/A	The first sample was diagnosed with Desquamative Gingivitis. The second and third samples were subjected to immunofluorescence	1st: Mouthwash (Kaopectate, Nystatin, Diphenhydramine, Lidocaine and Prednisolone).	The marginal erythema significantly subsided	12

			(five months ago). Nickel allergy.		margin of the surgical area.				desquamative gingivitis.		analysis and revealed no significant deposits of immunoglobulin, complement C3 or fibrin. The specimens were denuded of superficial epithelium, while the surrounding normal mucosa exhibited an intact epithelium.	2nd: incisional biopsy and corticosteroids		
Tomich et al., 1974	USA	40/F	N/A	Palate	N/A	5-10 years	N/A	N/A	Fibroma	N/A	N/A	N/A	N/A	N/A
		31/F	N/A	Inferior gingiva	N/A	12 months	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		16/M	N/A	Inferior gingiva	N/A	N/A	N/A	N/A	Fibroma	N/A	N/A	N/A	N/A	N/A
		N/A /F	N/A	Buccal mucosa	N/A	12 months	N/A	N/A	Papilloma	N/A	N/A	N/A	N/A	N/A
		45/M	N/A	Tongue	N/A	2 months	N/A	N/A	Mucocele	N/A	N/A	N/A	N/A	N/A
		28/M	N/A	Mandibular alveolar mucosa	N/A	N/A	N/A	N/A	Fibroma	N/A	N/A	N/A	N/A	N/A

		22/F	N/A	Palate	N/A	4 months	N/A	N/A	Mucocele	N/A	N/A	N/A	N/A	N/A
		19/F	N/A	Palate	N/A	4 months	N/A	N/A	Fibroma	N/A	N/A	N/A	N/A	N/A
Tobouti et al., 2018	Brazil	41/F	History of an oral surgery at the site of the current lesion (8 years ago)	Palate and Gingiva	Progressively growing and large-sized lesion. Well-defined, lobulated nodule covered by normal mucosa, firm on palpation and presented slight mobility	None 8 months	No changes were noted	3	Reactive injuries (peripheral ossifying fibroma, pyogenic granuloma, or peripheral giant cell granuloma). Salivary gland tumors	Alcian Blue: + S100: -	Well-delimited but non-encapsulated lesion, characterized by a myxomatous connective tissue presenting spindle-shaped fibroblasts interspersed with short bundles of collagen	incisional biopsy. And then surgical excision	No	8
Woo et al., 2015	Canada	2/F	Global developmental delay	Bilateral palate	Bilateral, pink, sessile masses, smooth, not ulcerated and firm to touch	Painless 3 months	No bone involvement	2 and 1.5 mean 1,75	Palatal exostosis, fibrous hyperplasia, peripheral ossifying fibroma, pleomorphic adenoma, lymphoma and Langerhans cell histiocytosis	N/A	Squamous mucosa overlying submucosa with a subepithelial band of myxoid tissue of low cellularity. The nuclei appeared spindled and bland	surgically excised	No	1
Yadav et al., 2016	India	25/F	None	Left posterior superior and left posterior Inferior gingiva	Pinkish red, firm, nontender dome-shaped mass	Painless 6 months	No bone involvement	1.5	Fibrous hyperplasia	N/A	Well-located areas of loose myxomatous connective tissue stroma surrounded by dense fibrous connective tissue. The myxomatous zone consisted of collagen fibrils and interposed widely spaced stellate-shaped fibroblasts	surgically excised	No	12

Supplementary Table 2. Critical appraisal of case series

Author(s)	Year	Were there clear criteria for inclusion in the case series?	Was the condition measured in a standard, reliable way for all participants included in the case series?	Were valid methods used for identification of the condition for all participants included in the case series?	Did the case series have consecutive inclusion of participants?	Did the case series have complete inclusion of participants?	Was there clear reporting of the demographics of the participants in the study?	Was there clear reporting of clinical information of the participants?	Were the outcomes or follow up results of cases clearly reported?	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	Was statistical analysis appropriate?
Aldred et al.	2003	Yes	No	Yes	Yes	No	Yes	No	No	Yes	No
Buchner et al.	1990	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No
Cunha et al.	2020	Yes	Yes	Yes	Yes	No	No	No	No	Yes	No
El Achkar et al.	2016	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No
Ena et al.	2013	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No
Gnepp et al.	1990	No	Yes	Yes	No	Yes	Yes	No	No	Yes	No
Gonzaga et al.	2018	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	No
Higuchi et al.	2019	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No
Madhusudhan et al.	2010	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No
Saito et al.	1985	No	Yes	Yes	No	No	Yes	No	No	Yes	No
Tomich et al.	1974	Yes	Yes	Yes	Yes	No	No	No	No	Yes	No

Supplementary Table 3. Critical appraisal of case reports

Author	Year of publication	Were patient's demographic characteristics clearly described?	Was the patient's history clearly described and presented as a timeline?	Was the current clinical condition of the patient on presentation clearly described?	Were diagnostic tests or assessment methods and the results clearly described?	Was the intervention(s) or treatment procedure(s) clearly described?	Was the post-intervention clinical condition clearly described?	Were adverse events (harms) or unanticipated events identified and described?	Does the case report provide takeaway lessons?
Agha-Hosseini et al.	2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Atarbashi-Moghadam et al.	2017	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Bharti et al.	2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bosco et al.	2014	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Camaron et al.	2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cho et al.	2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gabay et al.	2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Garcia et al.	2012	No	Yes	Yes	Yes	Yes	No	No	Yes
Germano et al.	2008	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Iezzi et al.	2001	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Joshi et al.	2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ko et al.	2019	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Kumar et al.	2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lee et al.	2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mattsson et al.	2017	Yes	No	Yes	Yes	Yes	No	No	Yes
Neto et al.	2014	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes

Niles et al.	2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pacifici et al.	2012	Yes	Yes	No	Yes	Yes	No	No	Yes
Pareek et al.	2019	No	Yes	No	Yes	Yes	No	No	Yes
Puna et al.	2013	Yes	Yes	No	Unclear	Yes	Yes	Yes	Yes
Silva et al.	2014	Yes	No	No	Yes	Yes	Yes	No	Yes
Soares de Lima et al.	2008	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Soda et al.	1998	Yes	No	No	Yes	Yes	No	No	Yes
Sowmya et al.	2015	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Taufiq et al.	2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tiwana et al.	2016	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Tobouti et al.	2018	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Woo et al.	2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Yadav et al.	2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

3 CONCLUSÃO

O presente artigo científico resumiu os principais dados sobre mucinose oral focal presentes na literatura, reunindo suas principais características clínicas, histopatológicas, radiográficas e demográficas. Identificando a predileção por sexo e idade, sintomatologia, assim como, apresentando a principal forma de tratamento, tipo de biópsia mais indicada, diagnósticos diferenciais clínicos e histológicos, recorrências e tempo de acompanhamento dos indivíduos. Além disso, o presente trabalho discutiu os dados existentes na literatura sobre as possíveis etiologias da MOF.

Essa revisão sistemática evidencia a importância da realização de exame complementar histopatológico, para diagnóstico de lesões em boca, e alerta para a realizações de biópsias quando necessárias.

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APÊNDICE A – REGISTRO PROTOCOLO PROSPERO – International prospective register of systemic reviews

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PROSPERO
International prospective register of systematic reviews

Oral focal mucinosis: a systematic review.

Manoela Martins, Larissa Dill, Lauren Schuch, Laura Kirschnick, Felipe Silveira

To enable PROSPERO to focus on COVID-19 submissions, this registration record has undergone basic automated checks for eligibility and is published exactly as submitted. PROSPERO has never provided peer review, and usual checking by the PROSPERO team does not endorse content. Therefore, automatically published records should be treated as any other PROSPERO registration. Further detail is provided **here**.

Citation

Manoela Martins, Larissa Dill, Lauren Schuch, Laura Kirschnick, Felipe Silveira. Oral focal mucinosis: a systematic review.. PROSPERO 2020 CRD42020215874 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020215874

Review question

The objective of the present study will be to integrate the available data published in the literature on oral focal mucinosis into a systematic review of the clinical, imaginological and histopathological features, treatment, recurrence frequency, differential diagnosis, risk factors and recurrence

Searches

Electronic searches will be made in databases, as following: Embase (Elservier), PubMed/MEDLINE (National Library of Medicine), SciELO (Scientific Electronic Library Online), Web of Science (Thomson Reuters), Mendeley, Scopus (Elsevier) and LILACS (Latin American and Caribbean Center on Health Sciences Information). Studies without publication date or in any language will be included. The search strategy that will be used is: (mucinoses OR mucinosis OR "oral focal mucinoses" OR "oral focal mucinosis") AND ("mouth" OR "oral cavity" OR "cavitas oris" OR "oral cavity proper" OR "mouth cavity proper" OR "cavitas oris propria"

Types of study to be included

It will be included all case reports and case series

Condition or domain being studied

The Oral Focal Mucinosis is an unusual pathology and few cases have been published in literature. The etiology of Oral Focal Mucinosis is still uncertain.

Participants/population

Individuals with Oral Focal Mucinosis.

Intervention(s), exposure(s)

Exposure: Oral Focal Mucinosis.

Comparator(s)/control

Not applicable

Main outcome(s)

Epidemiological, clinical and histopathological characteristics, and management of Oral Focal Mucinosis.

Measures of effect

None

Additional outcome(s)

Not applicable

Measures of effect

Not applicable

Data extraction (selection and coding)

The title and abstracts of all researched studies will be analyzed by two independent reviewers to determine if they meet eligibility criteria to be included. Possible disagreements between the two reviewers will be solved by a third one. Then, the analysis of the full texts versions will be made. For each of the included study, the following data will be obtained: (1) publication details (first author, year and country); (2) patients sex; (3) patients age; (4) anatomical location; (5) clinical presentation; (6) reported symptoms and duration; (7) histopathological pattern; (8) immunohistochemical expression; (9) treatment; (10) recurrence; (11) follow-up period; and (12) status.

Risk of bias (quality) assessment

Critical appraisal of the included articles was carried out by means of the Joanna Briggs Institute – University of Adelaide tool for case reports or case series (Gagnier JJ et al., 2013). The included articles were evaluated according to the following parameters: clear description of patient's demographic characteristics, medical history and current clinical condition, clear description of the propaedeutic data, treatment, post-intervention clinical condition, adverse events, and lessons provided by the case report.

Strategy for data synthesis

It will be provided a narrative synthesis of the findings from the included studies regarding the general characteristics of oral focal mucinosis reported in the included studies. The findings will be reported according to the data provided by the included studies.

Analysis of subgroups or subsets

Not applicable

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Dr Felipe Silveira. UNICAMP

Anticipated or actual start date

Risk of bias (quality) assessment

Critical appraisal of the included articles was carried out by means of the Joanna Briggs Institute – University of Adelaide tool for case reports or case series (Gagnier JJ et al., 2013). The included articles were evaluated according to the following parameters: clear description of patient's demographic characteristics, medical history and current clinical condition, clear description of the propaedeutic data, treatment, post-intervention clinical condition, adverse events, and lessons provided by the case report. The risk of bias will be considered low if all items will be present, medium if five or six items will be present, and high in the presence of four or fewer items.

Strategy for data synthesis

It will be provided a narrative synthesis of the findings from the included studies regarding the general characteristics of orofacial foreign body reactions reported in the included studies. The findings will be reported according to the data provided by the included studies. A qualitative synthesis will be performed according to the data extracted from the included studies.

Analysis of subgroups or subsets

Not applicable.

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UNICAMP Dr Vivian
Wagner. UNICAMP

Type and method of review

Diagnostic, Systematic review

Anticipated or actual start date

01 September 2020

Anticipated completion date

03 January 2021

Funding sources/sponsors

None.

Grant number(s)

State the funder, grant or award number and the date of award NA.

Conflicts of interest

Language

English

Country

Brazil

Stage of review

Review

Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

MeSH headings have not been applied to this record

Date of registration in PROSPERO

18 October 2020

Date of first submission

17 September 2020

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

18 October 2020