UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE ODONTOLOGIA

LUCAS GONÇALVES SANTOS

REAÇÕES DE CORPOS ESTRANHOS RELACIONADOS A PREENCHIMENTOS ESTÉTICOS OROFACIAIS: UMA REVISÃO SISTEMÁTICA

Porto Alegre

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

Orientadora: Profª. Drª. Manoela Domingues Martins

Porto Alegre

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DEDICATÓRIA

A este trabalho dedico à minha família, tanto aos que estão presente ao meu lado quanto àqueles que estão em minha cidade natal. Esta vitória dedico a vocês. Sem a ajuda de vocês, o meu sonho de tornar-me cirurgião dentista não teria acontecido.

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"[...] Acho uma tragédia quando aprendemos a valorizar o que temos só depois de perder. Acho uma tragédia não termos ido ainda para aquela viagem dos nossos sonhos. Acho uma tragédia viver de aparências. Acho uma tragédia ter comprado coisas achando que isso seria felicidade. Acho uma tragédia trabalhar em algo que você odeia. Acho uma tragédia você passar a vida brigado com alguém.

A morte não é uma tragédia. Tragédia é quando a gente não viveu. "

Marcos Piangers – Não é uma tragédia

RESUMO

Atualmente, diversos biomateriais de preenchimento têm sido utilizados na região orofacial para fins estéticos. No entanto, reações imunológicas e inflamatórias de longo prazo podem se desenvolver nos pacientes. Diante disso, o objetivo do presente estudo é revisar sistematicamente os dados clínico-patológicos referentes às reações de corpos estranhos relacionadas aos preenchimentos estéticos na região orofacial a partir da seguinte pergunta clínica: "Quais as principais características clínico-patológicas relacionadas a reações de corpo estranho que ocorreram em pacientes submetidos a procedimentos estéticos na região orofacial? ". Buscas eletrônicas foram realizadas em seis bases de dados convencionais (*Embase*, *Pubmed*, *Scopus*, *Medline Ovid*, *Web of Science* e *LILACS*) e duas bases de dados da literatura cinzenta (*Google Scholar* e *OpenGrey*). Além do mais, buscas manuais nas referências dos artigos incluídos foram realizadas. Os critérios de elegibilidade foram baseados em artigos sem qualquer restrição de língua ou publicação descrevendo relatos ou séries de casos de reações de corpos estranhos relacionados a preenchimentos orofaciais. Oitenta e quatro estudos reportando 137 casos clínicos foram identificados. A maioria dos casos foi publicada na América (n=71/51,9%). A média de idade ao diagnóstico foi de 53,63 anos variando entre 14 a 85 anos, com predileção por mulheres (n=128/94,2%). Em relação às suas principais características clínicas, nódulos (n=69/50,4%) e o lábio inferior representou a localização anatômica mais acometida (n=28/22,2%), seguido do lábio superior (n=27/21,6%). A remoção cirúrgica foi o tratamento de escolha (n=53/35,8%). O tempo médio entre a injeção e a reação foi de 58 meses, variando entre 10 dias a 40 anos. Os preenchimentos estéticos podem ocasionar em reações imunológicas e inflamatórias graves de longo prazo nos pacientes. Assim, o cirurgião-dentista deve ser capaz de reconhecer suas manifestações, principalmente porque o envolvimento orofacial pode representar um aspecto importante para o seu diagnóstico precoce e para o diagnóstico diferencial com outras condições clínicas na região orofacial.

Palavras-chave: Materiais Biocompatíveis, Reação a Corpo Estranho, Preenchedores Dérmicos, Revisão Sistemática.

ABSTRACT

Currently, several biomaterials have been used in the orofacial region for aesthetic purposes. However, long-term immune and inflammatory reactions can develop in patients. Therefore, the aim of the present study is to systematically review the clinicopathological data regarding foreign body reactions related to esthetic fillings in the orofacial region, based on the following clinical question: "What are the main clinical and pathological characteristics related to foreign body reactions that occurred in patients undergoing cosmetic procedures in the orofacial region?". Electronic searches were performed in six conventional databases (Embase, Pubmed, Scopus, Medline Ovid, Web of Science and LILACS) and two gray literature databases (Google Scholar and OpenGrey). Furthermore, manual searches of the references of the included articles were performed. Eligibility criteria were based on articles without any language or publication restrictions describing reports or case series of Foreign body reactions related to orofacial fillings. Eighty-four studies reporting 137 clinical cases were identified. Most cases were published in America (n=71/51.9%). The mean age at diagnosis was 53.63 years, ranging from 14 to 85 years, with a predilection for women (n=128/94.2%). Regarding its main clinical characteristics, nodules (n=69/50.4%) and the lower lip represented the most affected anatomical location (n=28/22.2%), followed by the upper lip (n=27/21 .6%). Surgical removal was the treatment of choice (n=53/35.8%). The mean time between injection and reaction was 58 months, ranging from 10 days to 40 years. Aesthetic fillings can lead to severe long-term immunological and inflammatory reactions in patients. Thus, the dentist must be able to recognize its manifestations, mainly because the orofacial involvement can represent an important aspect for its early diagnosis and for the differential diagnosis with other clinical conditions in the orofacial region.

Keywords: Biocompatible Materials, Foreign-Body Reaction, Dermal Fillers, Systematic Review.

LISTA DE ILUSTRAÇÕES

LISTA DE ABREVIATURAS

BC	Bovine Collagen
CAHA	Calcium Hydroxyapatite
CFO	Conselho Federal de Odontologia
FBP	Foreign Biopolimers
FBR	Foreign Body Reaction
FDA	Food and Drug Administration
HA	Hyaluronic Acid
HMMA	Hydroximetylmetacrylate
ISAPS	International Society of Aesthetic Plastic Surgery
PLLA	Polylactic Acid
PMMA	Polymethylmethacrylate
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
PROSPERO	Prospective Register of Systematic Reviews

SUMÁRIO

1 ANTECEDENTES E JUSTIFICATIVA

Segundo dados da Sociedade Brasileira de Cirurgia Plástica, os procedimentos estéticos não cirúrgicos aumentaram mais de 390% na população brasileira. Dentre os tratamentos mais realizados, constam os preenchimentos, uso da toxina botulínica, e o *peeling*. Além desses dados, o Brasil ocupa o segundo lugar no ranking de procedimentos estéticos não cirúrgicos no mundo todo, perdendo somente para os Estados Unidos (MENEZES A. J., 2017).

Em 2019, o Conselho Federal de Odontologia (CFO) pela Resolução 198, reconhece a Harmonização Orofacial como especialidade odontológica e dá outras providências. Conforme consta na Resolução 198 (2019, art. 3°, p.2), as áreas de competência do Cirurgião-Dentista especialista em Harmonização Orofacial, incluem:

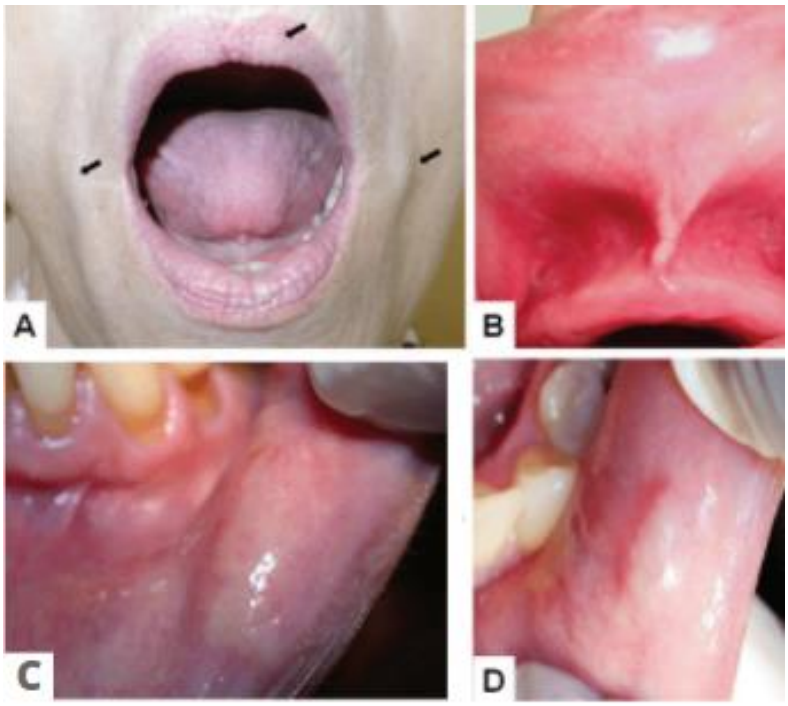
> 6. b) fazer uso da toxina botulínica, preenchedores faciais e agregados leucoplaquetários autólogos na região orofacial e em estruturas anexas e afins; 8. d) fazer a intradermoterapia e o uso de biomateriais indutores percutâneos de colágeno [...] 9. f) realizar tratamento de lipoplastia facial, [...], técnica cirúrgica de remoção do corpo adiposo de Bichat (técnica de Bichectomia) e técnicas cirúrgicas para a correção dos lábios (*liplifting*) na sua área de atuação e em estruturas relacionadas anexas e afins.

Os preenchimentos estéticos começaram a ser elaborados há muitos anos atrás, e a *Food and Drug Administration* (FDA) é o principal órgão internacional responsável para aprovação e seleção destas substâncias para uso na população. O colágeno bovino foi a primeira substância aprovada, em 1981, para aplicação na região occiptofrontal, temporal, glabela e zigomático para correção dos contornos faciais (KLEIN A.W., ELSON M.L., 2000; COUGHLIN A. *et al*., 2020). Atualmente, os preenchimentos existentes podem ser divididos como reabsorvíveis, os quais são degradados ao longo da vida, compostos pelo colágeno bovino, ácido hialurônico, hidroxiapatita de cálcio e o ácido poliláctico, e os não reabsorvíveis, os quais se mantém na localização anatômica ao longo da vida, sem capacidade de degradação, como o polimetilmetacrilato, o único preenchedor não reabsorvível aprovado pela FDA para uso na população (BALLIN A.C. *et al*., 2015; COUGHLIN A. *et al*., 2020).

Apesar da segurança e sucesso dos procedimentos envolvendo o uso de preenchedores, reações adversas podem ocorrer – e têm sido cada vez mais relatadas. Diante da crescente procura por essas técnicas, tem aumentado também o reporte de

casos apresentando erros ou sequelas do tratamento (ALCÂNTARA C. E. P. *et al*., 2018; REQUENA L. *et al*., 2011; ROLIM L. S. A. *et al*., 2019). As manifestações clínicas mais comumente encontradas são lesões inflamatórias aos quais ocorrem formação de corpo estranho, acompanhadas ou não de alguns sinais clínicos como, por exemplo, edema, prurido, dor, formação de nódulos em alguns casos e migração do material preenchedor, como exemplificado na figura 1 (ESTEVES A.L. *et al*., 2016).

Figura 1 - Casos Clínicos de Reações de Corpos Estranhos



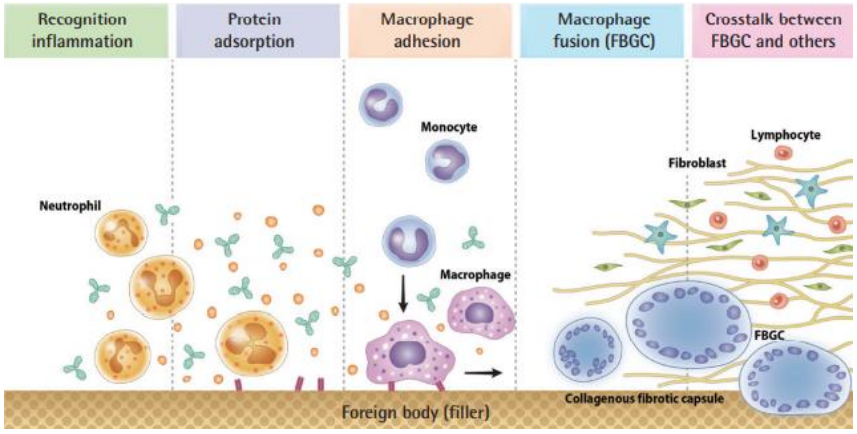
Fonte: Esteves A.L. et al. (2016)

Reações de corpos estranho são causados por inflamação granulomatosa após a agregação de macrófagos em resposta a biomateriais que não podem ser fagocitados. A reação começa com a infiltração de neutrófilos, macrófagos e a adsorção instantânea de várias proteínas do hospedeiro para o biomaterial. Leucócitos polimorfonucleares circulantes, principalmente neutrófilos, movem-se para o tecido como a primeira linha de defesa; se os neutrófilos são incapazes de fagocitar a partícula, os macrófagos assumem um papel mais dominante no processo (BENTKOVER S.H., 2009). Os biomateriais imediatamente recebem uma camada de proteínas do hospedeiro antes de interagir com as suas respectivas células de defesa. A presença dessas proteínas adsorvidas modulam a inflamação do hospedeiro e a resposta de cicatrização. Propriedades físicas, como tamanho da partícula, formato da superfície da partícula,

carga superficial e concentração de partículas podem influenciar na sua fagocitose (BENTKOVER S.H., 2009; LEE, J. M., KIM Y. J., 2016). Os macrófagos podem ingerir até 25% de seu volume por hora e o tamanho da partícula é importante na fagocitose; porém, não é o único determinante de uma fagocitose eficaz. No caso em que o volume da partícula é maior que o volume de um macrófago, a agregação do macrófago é necessária e células gigantes de corpo estranho são formadas (FREITAS R. A. *et al*., 2003; LEE, J. M., KIM Y. J., 2016).

A progressão dos eventos de inflamação requer o extravasamento e a migração dos monócitos do sangue em resposta a quimiocinas e outros quimioatratentes para o local anatômico preenchido por biomaterial, se diferenciando em macrófagos. Macrófagos e células gigantes de corpo estranho secretam uma série de mediadores inflamatórios que serão capazes de secretar fatores de crescimento e fatores angiogênicos, os quais são importantes na regulação de fibroblastos. Os macrófagos, através de uma cascata de sinalização, recrutam e ativam fibroblastos, e uma cápsula fibrosa se desenvolve em torno do material preenchedor (ANDERSON J.M., RODRIGUEZ A., CHANG D.T., 2008). A figura 2 ilustra o processo de formação da reação de corpo estranho.

Figura 2 – Etiopatogênese da reação de corpo estranho



Fonte: Lee, J. M., Kim Y. J. (2016)

Com base nos diversos produtos de preenchimento estético existentes nos dias de hoje, diversos materiais cosméticos podem ser encontrados na literatura aos quais provocaram reações adversas nos pacientes nas mais diversas áreas anatômicas da face (ALIJOTAS R. J. et al., 2009; FARAHANI S. S. *et al*., 2014). Cada material cosmético possui especificidade com relação ao tempo e modo de aplicação distintos,

uma vez que cada material possui diferentes partículas e propriedades físico-químicas, como por exemplo, hidrofilidade, carga superficial da partícula, suavidade da partícula, bem como o nível de biocompatibilidade com tecidos epiteliais e tecido conjuntivo (LEMPERLE G. et. Al., 2009; LEE, J. M., KIM Y. J., 2016).

É necessário que o profissional possua uma capacidade de lidar com essas possíveis complicações reconhecendo-as através de uma cuidadosa anamnese, por meio de minuciosa análise das características clínicas e histopatológicas da lesão, para evitar erros de diagnóstico com outras possíveis lesões clinicamente semelhantes, como mucoceles ou neoplasias benignas, e tratá-las de forma adequada (ESTEVES A.L. *et al.*, 2016; ROLIM L. S. A. *et al*., 2019). O conhecimento destas lesões pelo cirurgião dentista é fundamental, pois este é frequentemente o primeiro profissional a ser procurado pelo paciente para o diagnóstico de lesões na região orofacial. Neste contexto, devido à grande variabilidade de materiais preenchedores, bem como a inserção cada vez maior da Odontologia no âmbito de procedimentos estéticos não cirúrgicos na região orofacial associado ao aumento no número de procedimentos nas últimas décadas, o objetivo deste trabalho é de integrar todos os dados clínicos e histopatológicos disponíveis na literatura através de uma revisão sistemática para responder a seguinte pergunta clínica: “Quais as principais características clínico-patológicas relacionadas a reações de corpo estranho que ocorreram em pacientes submetidos a procedimentos estéticos na região orofacial?”.

2 ARTIGO CIENTÍFICO

Foreign body reactions related to orofacial aesthetic fillers: a systematic review

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ABSTRACT

Introduction: Several biomaterials have been used in the orofacial region for aesthetic purposes. Still, in some cases severe long-term immune and inflammatory reactions can develop in some patients.

Objective: To systematically review the clinicopathological data regarding foreign body reactions (FBR) related to aesthetic procedures in the orofacial region.

Material and methods: Electronic searches were performed in six databases and in gray literature according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Eligibility criteria were based on articles without any language or publication restrictions describing case reports or case series of FBR related to orofacial aesthetic procedures.

Results: Eighty-four studies reporting 137 cases of FBR were identified. The mean age at diagnosis was 53.63 years (14 to 85 years), with most of the cases reported in America (n=71/51.9%) and mainly occurring in women (n=128/94.2%). Nodules were the main clinical characteristics, (n=69/50.4%) presented as nodules and the most cases presented as asymptomatic (n=59/43.49%). The lower lip represented the most affected anatomical location (n=28/22.2%), followed by the upper lip (n=27/21, 6%). Surgical removal was the treatment of choice (n=53/35.8%). Twelve different dermal fillers were reported in the study, and the histopathological features were described regarding the particle size, particle surface shape, surface charge and particle concentration itself.

Conclusion: Nodule and swelling were the main clinical characteristics of FBR related to orofacial aesthetic fillers, with its histological characteristics depending on the type of the filler material used. Health professionals must be able to recognize its manifestations and perform an accurate differential diagnosis.

Keywords: Biocompatible Materials, Foreign-Body Reaction, Dermal Fillers, Systematic Review.

1. Introduction

Foreign body reactions (FBR) are immunologic and inflammatory reactions that can occur in some patients after receiving biomaterial grafting. The condition is usually characterized by a long-term clinical responses and can be associated to the presence of redness, pain, itching, oedema, and nodule formation in the affected area (LEE, KIM, 2016). Several major retrospective and prospective studies in the literature demonstrate cases of FBR in patients submitted to aesthetic procedures in the orofacial region (**Supplementary Table 1**) (JHAM et al., 2009; REQUENA et al., 2011; DALEY et al., 2012). Due to the increase of nonsurgical aesthetic procedures in the orofacial region, clinical cases involving FBR are being increasingly reported in the literature (ALCÂNTARA et al., 2018; ROLIM et al., 2019).

The etiopathogenesis related to FBR involves the infiltration of neutrophils, macrophages, and instantaneous adsorption of various host proteins onto the inserted biomaterial (WANG et al., 2018). The presence of these adsorbed proteins modulates host inflammation and the healing response. Physical properties such as particle size, particle surface shape, surface charge and particle concentration can influence its phagocytosis (BENTKOVER, 2009; LEE, KIM, 2016). In some cases, where the particle volume is greater than the volume of the recruited macrophages, a macrophage aggregation is necessary resulting in clinical manifestations of FBR (FREITAS et al., 2003; LEE, KIM, 2016).

The International Society of Aesthetic Plastic Surgery (ISAPS) reports worldwide recrudescent search for aesthetic surgery with nonsurgical procedures increasing 7.4% in 2019 at the latest global survey (ISAPS, 2019). According to this survey, botulinum toxin and hyaluronic acid (HA) are the most popular biomaterials used for nonsurgical procedures nowadays. As reported by the Food and Drug

Administration (FDA), biomaterials are divided in resorbable, which are degraded throughout the life - such as bovine collagen (BC), HA, calcium hydroxyapatite (CAHA) and polylactic acid (PLLA) fillers; and non-resorbable, which remain in the initially inserted anatomical location throughout the life, such as polymethylmethacrylate (PMMA), the only non-resorbable filler approved by FDA for use in humans (KLEIN, ELSON, 2000; BALLIN et al., 2015; COUGHLIN et al., 2020). However, the use of yet non-approved fillers is reported in the literature, such as hydroximetylmetacrylate (HMMA) (BROLY et al., 2020), foreign biopolimers (FBP) (JHAM et al., 2009), vitamins (ANASTASSOV et al., 2008; KAMOUNA et al., 2015), and silicone (FICARRA et al. 2002; GONÇALVES et al., 2009; WULU et al., 2019).

The knowledge on the main characteristics of the adverse effects of nonsurgical aesthetic procedures at the orofacial region is essential to deal with possible complications inherent to the technique (ALIJOTAS et al., 2009; FARAHANI *et al.*, 2012). In this sense, recognizing the main clinical and histopathological characteristics of FBR is important to avoid differential diagnostic pitfalls (ESTEVES et al., 2016; ROLIM et al., 2019). To the best of our knowledge, no systematic reviews of previous published cases of FBR related to orofacial aesthetic fillers to integrate all the available data to support this association are current available in the literature. Therefore, this systematic review aimed to answer the following review question: “What are the clinicopathological characteristics related to FBR occurring in patients submitted to orofacial aesthetic procedures?”.

2 Material and Methods

2.1 Eligibility criteria

2.1.1 Inclusion criteria

The Population (P), Intervention (I), Comparison (C), Outcome (O), and Study design (S) – PICOS approach was used as a strategy to elaborate the question of this systematic review, as follows: P: individuals with the development of FBR after aesthetic procedures in the orofacial region; I: orofacial dermal fillers; C: not applicable; O: clinicopathological data regarding FBR related to orofacial dermal fillers; S: case reports and case series. The case reports and case series included in this systematic review should involve the use of no autogenous orofacial liquid fillers reporting its related adverse events due to the aesthetic procedures with FBR formation and detailed presentation of the clinical and histopathological characteristics of the lesions.

2.1.2 Exclusion criteria

Animal, laboratory studies, opinions or commentaries, conference abstracts, letters, short surveys, and reviews were excluded. In addition, studies that involved solid or semisolid exogenous orofacial fillers or autogenous fillers; studies that assessed the quality of biomaterials; surgical aesthetic procedures; studies with the development of FBR in a region different from the orofacial region and studies without sufficient clinical and histopathological analyses were also excluded.

2.2 Information sources and search strategy

Systematic electronic searches without publication date or language restriction were undertaken in August 2020, and updated in July 2021, in the following electronic

databases: PubMed, Scopus, Web of Science, Medline Ovid, Embase and LILACs. An additional search in the Gray literature including Google Scholar and OpenGrey were also recorded. Search strategy was composed of controlled predefined Medical Subject Heading (MeSH) terms and free terms using the Boolean operators (*i.e.*, OR, AND), always adapting to the syntax rules of each electronic database to identify relevant studies. The detailed search strategy is demonstrated in **Supplementary Table 2**. Additional manual searches were also conducted by cross-checking the reference lists of the included articles for the identification of publications that might have been missed during the searches in the electronic databases. EndNote X9 (Thomson Reuters, Philadelphia, PA) was the used to manage all the references recorded in the selection process of this study.

2.3 Study selection

The included studies were selected through a two-phase selection process. First, two independently reviewers (L.G.S. and L.C.J.) screened the titles and abstracts of the articles selected using the software reference manager (EndNote X9). The studies that did not meet the inclusion criteria, were automatically excluded. In the second phase, both reviewers read the full-text articles of the studies selected in the first phase. The studies containing all the inclusion criteria were finally included in this systematic review. At the end phase of both selection process, a reunion was made between both reviewers and, in case of discordance, a third (L.F.S.), or even a fourth (F.M.S) reviewer was consulted.

2.4 Data collection process

The following data (when available) were extracted on a standard form from each included study by two reviewers (L.G.S. and L.C.J): (1) information regarding author(s) and publication data (year and country), (2) patient's age and (3) sex, (4) anatomical location of the procedure, (5) clinical presentation, (6) reported duration, (7) reported symptoms, (8) type of biopsy, (9) histopathological features, (10) time between injection and reaction, (11) treatment, (12) recurrence, (13) type of dermal fillers used, (14) follow-up period, and (15) clinical and histopathological differential diagnosis.

2.5 Risk of bias

The risk of bias was assessed by two reviewers (L.G.S. and L.C.J.) using the Joanna Briggs Institute Critical Appraisal Checklist - University of Adelaide tool for case reports or case series (GAGNIER 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.

2.6 Synthesis methods

This systematic review presented a detailed quantitative synthesis of the results presented by the included studies.

2.7 Other information

This systematic review registered in the Prospective Register of Systematic reviews (PROSPERO; Center for reviews and Disseminations, University of York, registration number CRD42020209942); and carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (PAGE et al., 2020).

3 Results

3.1 Study selection

A total of 1,129 records were identified through the initial database searching, and 686 records were maintained in the selection process after the removal of the duplicates. In phase-one, titles, and abstracts of all 686 articles were assessed and one study screened from the grey literature, and 192 articles were eligible for the next phase. In phase-two, 83 studies were included after full text assessment of the articles, and one study found in the references were also included by manual search, totalizing 84 studies included in this systematic review. The complete identification to the inclusion of the articles is provided in **Figure 1**. Furthermore, the reasons for exclusion of each article are presented in **Supplementary Table 3**.

3.2 Study type and origin

The results of the present systematic review are summarized in **Table 1**. All included papers were classified as case series or case reports, resulting in a total of 137 cases published from 1967 to 2020 in three different continents. The United States was the most common country of origin of studies (n=39/28.5%), followed by Brazil (n=32/23.4%).

3.3 Clinical characteristics

Women were more affected (n=129 cases/94.20%) than men (n=8/5.80%), with a mean age of 53.63±12.35 years old (ranging from 14 to 85 years old). The most common clinical presentation described was a nodule (n=69/50.40%), followed by a swelling occurring in the anatomical location of the procedure (n=39/28.50%). Masses into the submucosal tissue were reported (n=11/8.00%) and ulcers were reported in 3 (2.20%). Most cases were asymptomatic (n=59/43.49%) but 41 cases (30.01%) were associated to symptoms such as pain, itching, pruritus, or pus in the area. Duration of the lesions varied from 0.10 to 96 months with a mean of 13,49±19,47 months.

Figure 1. Flowchart

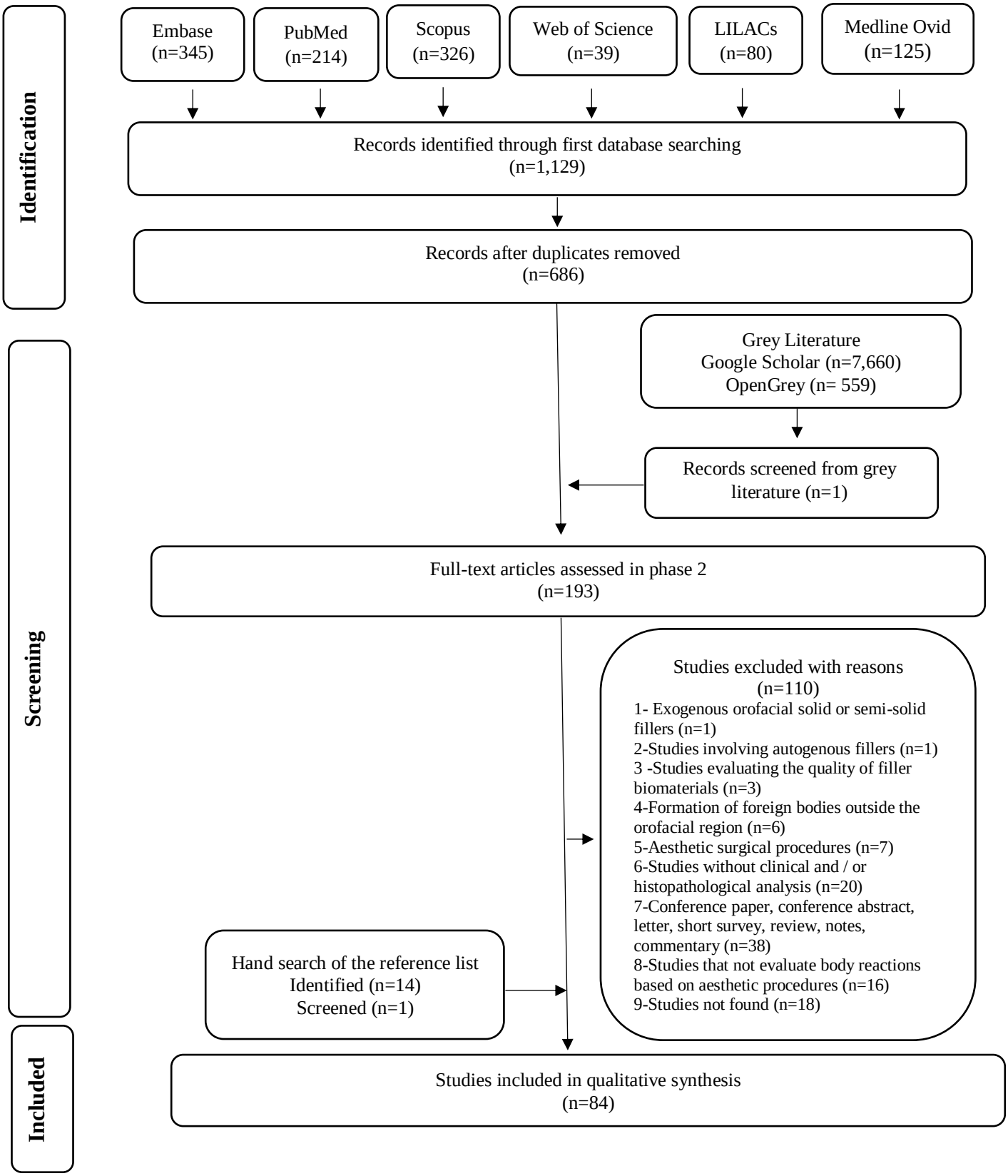

Table 1. Demographic and clinical features of foreign body reactions clinical cases included in the present systematic review

Variable	n (%)
Continent (n=137)	
America	74 (54.30)
Europe	52 (37.80)
Asia	11 (7.90)
Sex (n=137)	
Female	129 (94.20)
Male	8 (5.80)
Age (years) (n=137)	
Mean (SD)	53.63 (±12.35)
Range	14 - 85
Reported duration (months) (n=66)	
Mean (SD)	13 (±13.49)
Range	0.1 – 96.00
Anatomical location (n=151)*	
Lower lip	28 (22.20)
Upper lip	27 (21.60)
Cheeks	18 (10.50)
Nasolabial folds	16 (9.40)
Periocular	14 (8.20)
Multifocal	10 (5.80)
Mandible	7 (4.10)
Forehead	6 (3.50)
Melolabial folds	6 (3.50)
Chin	5 (2.90)
Buccal mucosa	4 (2.30)
Glabella	3 (1.80)
Zygomatic	3 (1.80)
Nose	1 (0.60)
Paranasal	1 (0.60)
Peribuccal	1 (0.60)
Temporal	1 (0.60)
Clinical features (n=137)	
Nodule	69 (50.40)
Swelling	39 (28.50)
Mass	11 (8.00)
Papule	6 (4.40)
Ulcers	3 (2.20)
Eczema	2 (1.50)
Inflammatory lesion	2 (1.50)
Oedema	2 (1.50)
Plaque	2 (1.50)
Erythema	1 (0.50)
Symptomatology (n=137)	
No	59 (43.40)
Yes	41 (30.10)
NI	37 (26.50)
Type of Biopsy (n=136)	
Excisional	46 (33.80)
Incisional	46 (33.80)
NI	33 (24.30)
Punch	11 (8.10)
Treatment (n=148)**	
Surgical removal	53 (35.80)
Corticosteroids	37 (25.00)

NI	32 (21.40)
Antibiotics	9 (6.10)
Hyaluronidase	6 (4.10)
Anti-inflammatory	4 (2.70)
Allopurinol	2 (1.40)
Preservation	2 (1.40)
Imiquimod	1 (0.70)
Laser Therapy	1 (0.70)
Methotrexate	1 (0.70)
Types of dermal fillers (n=139)* **	
Hyaluronic Acid	40 (28.80)
Silicone	37 (26.60)
Polymethymethacrylate	17 (12.20)
Poly – L – lactic Acid	9 (6.50)
Bovine Collagen	8 (5.80)
Polyacrilamide Gel	7 (5.20)
Calcium Hidroxiapatite	6 (4.30)
Foreign Biopolymer	6 (4.30)
Bio-Alcamid	2 (1.40)
Bioplastique	2 (1.40)
Vitamins	2 (1.40)
NI	2 (1.40)
Hydroxymethylmetacrylate	1 (0.70)
Time between injection and reaction (months) (n=106)	
Mean (SD)	58.69 (±80.62)
Range	0.10 – 480.00
Recurrence (n=137)	
NI	67 (48.50)
No	50 (36.80)
Yes	20 (14.70)
Follow-up (months) (n=43)	
Mean (SD)	14.97 (±13.32)
Range	1.10 – 72.00

NI, not informed.
*Some cases reported more than one anatomical location.
**Some cases reported more than one treatment.
*** Some cases reported more than one dermal filler.

3.4 Anatomical location

Among the orofacial regions affected, most of the cases occurred in the lips, mainly the lower lip (n=28/22.2%) followed by the upper lip (n=27/21.6%). Cheeks, nasolabial folds and the periocular regions were reported in 18 cases (10.5%), 16 cases (9.4%) and 14 cases (8.2%), respectively.

3.5 Types of dermal fillers used

Twelve different types of dermal fillers were reported in the cases included in the present systematic review, with HA (n=40/29.2%) and silicone (n=37/26.60%) being the most

used. PMMA was reported in 17 cases (12.4%) and other dermal fillers were also used, such as BC, CAHA, PLLA, bio-alcamid, bioplastique, FBP, polyacrylamide gel and vitamins injection. The time between the injection of the fillers and the development of the FBR was available in 106 cases and varied from 0.10 to 480 months, with a mean time of 58±80.62 months.

3.6 Type of biopsies

Biopsies were performed to confirm the diagnosis in 103 cases, including excisional biopsies (n=46/33.80%), incisional biopsies (n=46/33.80%) and 11 (8.10%) punch biopsies.

3.7 Histopathological characteristics

The histopathological features varied according to the material used and are described in **Supplementary Table 4**. Patients that received HA presented a very similar histological pattern composed of dense, amorphous, acellular, basophilic and eosinophilic materials between epithelium and subcutaneous tissue with variable size surrounded by numerous histiocytic/macrophages and multinucleated foreign body granulomatous reaction in a chronic immunologic and inflammatory environment. Bio-alcamid has a similar characteristic with the presence of multiple foreign body type granulomas and chronic inflammation within a loose connective tissue matrix.

The silicone, bioplastique and FBP's cases generally presented as vacuoles, cavities or even pseudocystic components with distinct shapes and size through the epithelium and subcutaneous tissue, surrounded by numerous lymphocytes, macrophages and giant cells. Injections of vitamins were composed of dense inflammatory reaction with numerous ovoid cavities invading the dermis. All these related dermal fillers resulted in a "Swiss cheese" appearance.

CAHA's histological features has a unique presentation of microspheric foreign bodies showing a crackled appearance with amorphous materials of black staining inside accompanied by chronic inflammation with epithelioid histiocytices and giant cells.

PMMA's histological pattern were mostly composed as small uniformly vacuoles of homogeneous shape and size, surrounded by a diffuse granulomatous reaction and chronic inflammatory cells.

PLLA cases were histologically characterized with at least two different types of extracellular materials with evidence of dense formation of FBR with abundant collagen formation around of several histiocytic cells and giant cells associated with numerous small vacuoles with the same shape and size.

BC cases presented a lack of lymphocytes and histiocytes with infiltrated giant cells and epithelioid cells. It contained numerous cells with clear, often multiple, cytoplasmic vacuoles, displacing a single peripheral nucleus. Showing similar histologic features as hyaluronic acid FBR formation.

Polyacrilamide gel cases presented as an amorphous basophilic material being engulfed by foreign body giant cells, forming granulomas amidst histiocytic inflammatory infiltrate.

3.8 Clinical and histopathological differential diagnosis

Clinical differential diagnosis included mucocele, soft tissue benign neoplasms without specification, minor salivary glands benign neoplasms, sclerotic/inflamed minor salivary gland, and fibrous hyperplasia, among others. Histopathological differential diagnosis included mucoepidermoid carcinoma, low grade lipossarcoma, sarcoidosis, mucosal cysts, Wegener granulomatosis, and acute cytomegalic inclusion disease, among others. The

complete list with the clinical and histopathological differential diagnosis is demonstrated in **Table 2.**

Table 2. Clinical and histopathological differential diagnosis

Hypothesis of Diagnosis	**n (%)**
Clinical differential diagnosis (n=26)	
Mucocele	6 (15.00)
Benign neoplasm	4 (10.00)
Neoplasia of minor salivary glands	3 (7.50)
Fibrous hyperplasia	2 (5.00)
Sclerotic/inflamed minor salivary gland	2 (5.00)
Encapsulated collagen	1 (2.50)
Facial granulomatosis	1 (2.50)
Fibroma	1 (2.50)
Idiopathic angioedema	1 (2.50)
Leukoplakia	1 (2.50)
Nerve sheath tumor	1 (2.50)
Non-specific chronic inflammatory process	1 (2.50)
Salivary gland adenoma	1 (2.50)
Soft tissue neoplasm	1 (2.50)
Histopathological differential diagnosis (n=14)	
Lipossarcoma	3 (7.50)
Sarcoidosis	2 (5.00)
Mucoepidermoid carcinoma	2 (5.00)
Mucosal cyst	2 (5.00)
Acute cytomegalic inclusion disease	1 (2.50)
Encapsulated collagen	1 (2.50)
Morbus Wegener granulomatosis	1 (2.50)
Toxoplasmosis	1 (2.50)
Tuberculosis	1 (2.50)

3.9 Treatment

Most patients were managed by surgical removal of the lesions (n=53/35.80%), followed by the use of systemic medications, mostly steroids (n=37/25.00%), antibiotics (n=9/6.10%) and anti-inflammatories (n=4/2.70%). Moreover, in six cases the patients were treated with hyaluronidase (4.10%), exclusively for hyaluronic acid dermal fillers cases. In addition, laser therapy, methotrexate, imiquimod and allopurinol were reported by other studies. Treatment method was not described in 32 cases (21.60%).

3.10 Follow-up and recurrence

Forty-three cases presented follow-up, with a mean of 14.97±13.32 months, and four cases was lost to follow-up (2.90%). The majority of the cases did not suffer recurrence (n=50/71.40%) and twenty had recurrence (n=20/28.60%).

3.11 Risk of bias

Critical appraisal of the case reports provided clear description of patient's demographic characteristics and current clinical condition of the patients, as well as the histopathological analysis and takeaway lessons. Details of the current history condition of the patients and adverse events (harms) or unanticipated events were not clearly reported. Complete inclusion and clinical information of the participants was clearly reported in all case series. The criteria of inclusion, methods used for identification of the condition for all participants included and the presentation site(s)/clinic(s) demographic information were described in most case series. Statistical analyses and the outcomes or follow up results of cases were poorly reported. The critical appraisal of the case series and case reports is displayed in **Supplementary Table 5 and 6**.

4 Discussion

The total number of nonsurgical aesthetic procedures performed worldwide in the latest global survey, in 2019, is nearly 11 million (ISAPS, 2019). The use of these products is growing exponentially due to several factors. However, despite the demonstrated safety following the use of these agents, complications and adverse events can also occur (JONES, 2006; COHEN, 2008; JONES et al., 2021). In the present systematic review, 137 cases of FBR were analyzed bringing the main clinical and histopathological characteristics and the management of these complications.

Our results demonstrated that FBR affected more females with an average age of 56.63 years old. This data is in accordance with the literature, which shows that facial aesthetic filling procedures are mostly performed in women around the sixth decade of life (JHAM et al., 2009; ROLIM et al., 2019). Also, regarding the site of development of FBR it was expected that the lip region would be the most affected because nowadays, lips and eyes are orofacial regions considered the most important facial elements to beauty ideals for both males and females around the world. Under these circumstances, the perception of beauty by the population induces people to look forward aesthetic medical procedures (REDAELLI et al., 2020).

The main clinical manifestation of FBR reported were nodules and swelling (78.9%) with 43.49% of the cases being asymptomatic. However, in 30.01% symptoms such as pain, itching, pruritus, and purulent discharge in the area were described. According to the literature, the clinical manifestation of FBR induced by aesthetic fillers will depend on the chemical composition of the cosmetic used, systemic condition of the patient and how the technique is applied (JHAM et al., 2019; ROLIM et al., 2019). Those three factors can be considered determinant on how the clinical and the histopathological manifestations will present. Following the chemical composition of the cosmetic used, the particle size, particle surface shape, surface charge and particle concentration are mandatory to differentiate and to determine which type of dermal filler was used. For example, silicone, bioplastique and FBP generally presented particles with heterogeneous distinct shapes and size, whereas PMMA presents uniformly particles of homogeneous shape and size. In addition, the presence of acute and chronic inflammation is a pathophysiology process of the organisms presented in any case of FBR. Usually, the inflammatory process in response to dermal fillers is chronic but few patients could develop more acute and symptomatic reaction (LEE, KIM, 2016; WANG et al., 2018). Moreover, the technique applied frequently determines the clinical

aspects of the lesions and the health professionals needs to pay attention of different areas during these nonsurgical aesthetic procedures to guarantee the best result for the patient and avoid possible formation of FBR (PHILIPP-DORMSTON et al. 2020). The common technical errors leading to filler complications included improper volume (too much or too little), improper depth (superficial or deep), wrong location (unfavorable or incorrect anatomic location), and inappropriate material (DELORENZI, 2013)

Regarding the clinical differential diagnosis our findings indicated that clinicians included mainly lesion with benign behavior such as mucocele or benign neoplastic process of soft tissue or salivary gland origin. These hypotheses are adequate since these lesions also manifests as asymptomatic nodules or swellings with smooth, non-ulcerated surface, slow and localized growth with well delimited borders (VALÉRIO et al., 2013; SILVA et al., 2019)

Histologic characteristics of FBR depended exclusively on the type of the particles of the filler's materials injected. Also, a correlation between microscopic findings and histopathological differential diagnostic needs to be recognized. Microscopically, some authors have emphasized that some dermal fillers, for example, liquid silicone and PMMA, should be considered in the histopathological differential diagnosis of malignant tumors. Cytoplasmatic vacuoles and histocytes with variables shapes can mimic adipocytic tumors, such as low grade liposarcoma, or even mucoepidermoid carcinomas (MALY et al., 2004; KARAGOZOGLU et al., 2008; GONÇALVES et al., 2009; KACZOROWSKI et al., 2020). Therefore, additional analysis was performed in some cases, including radiographs, laboratory tests, immunohistochemistry, and electron microscopy.

Another important aspect to be discussed is the collaboration of the patients regarding clinical history. It was possible to observe that most of the patients confirmed nonsurgical aesthetic procedures previously. However, in some studies included, patients did not inform or omit information if they had a previous aesthetic intervention (DALEY et al., 2012;

ROLIM et al., 2019), as well as patients who remembered that had undergone an aesthetic procedure, but only confirm after interrogation with the histopathological results. Therefore, accurate anamnesis needs to be performed when FBR related to aesthetic procedures is a hypothesis of diagnostic.

Regarding the management of these complications, surgical removal was the treatment of choice for the most cases. Throughout the data collection process was possible to notice an influence in the necessity of a biopsy to reach a final diagnostic of FBR related to aesthetic procedure. Based on clinical hypotheses, excisional or incisional biopsies are often performed to guarantee the best approach, with a diagnostic accuracy varying between 88% and 100% (CLAYER, 2010; KASRAEIAN et al., 2010; MOHR et al., 2012), suggesting the considerable number of surgical procedures fulfilled. In contrast, Drs Lemperle and Gauthier-Hazan (2009) pointed the treatment of choice for FBR after injectable dermal fillers the intralesional injections of corticosteroids associated or not with antimitotic agents. According to this study, those medications are effective because it can act at the pathophysiology process of FBR decreasing both cellular proliferation and invasion including collagen production by fibroblasts and being less invasive. Thus, our systematic review demonstrated that surgical removal was made especially in single region of the face and nodularity cases. Patients that presented swellings and nodularity in multifocal regions, the treatment of choice was medication therapy.

Although many results were obtained, our data must be interpreted with caution and limitations. Most of the selected studies did not mention follow-up. Clinicians have difficulties to follow-up the patients, which consequently difficult the assessment of recurrence. These variables are limitations that can be found along clinical studies in the literature and necessitates encouragement to inform at least how complete their follow-up was (ALLMEN et al., 2015). In addition, the majority selected studies were case reports and some

of them were case series. In most case series, it is likely that some cases included in case series did not match with the inclusion criteria of this study. Therefore, minucious analyses of the case reports presented at the case series were made, hence some cases were excluded. Beyond that, postoperative analyses, such follow-up, recurrences, and differential diagnoses were not taken into account in the published literature.

Conclusion

In the present systematic review, FBR related to orofacial aesthetic fillers were most characterized as nodularity and swelling, occurring most in female individuals of the sixth decade of life and located at lips. The clinical manifestations can be quite unspecific, and a thorough anamnesis is of paramount importance to guide the differential diagnosis. Its histological characteristics seem to depend on the particle size, particle surface shape, surface charge and particle concentration of the cosmetic material used. Even so, the morphological features can usually guide or accurately determine the diagnosis of FBR. A correct knowledge about the technique and the correct formation of the professional are vital to prevent these reactions. Is also important to incorporate these pathologies as lessons to dentistry and medicine schools to enable spread information.

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Supplementary Table 1. Major prospective and retrospective studies of FBR

Author, Year	Country	Number of Cases	Center	Male	Female	Mean Age	Mean Follow-up
Alijotas-Reig and Garciaz 2008	Spain	25	Clinical Immunology Unit andmembers of the scientific committee of the Sociedad Española de Medicina y Cirugia Cosmética (Spanish Society of Cosmetic Medicine and Surgery)	NI	NI	NI	16 months
Alijotas-Reig et al., 2009	Spain	10	Clinical Immunology Unit andmembers of the scientific committee of the Sociedad Española de Medicina y Cirugia Cosmética (Spanish Society of Cosmetic Medicine and Surgery)	0	10	42, Range 34 - 55	20.1 months
Alijotas-Reig et al., 2009	Spain	10	Department of Internal Medicine I, Vall d'Hebron University Hospital, and Aging Basic Research Group, Molecular Biology and Biochemistry Research Centre for Nanomedicine	0	10	42, Range 31 - 65	50.2 months
Artzi et al., 2016	Israel	400	The Sackler School of Medicine	40	360	49.6	11 months
Bachmann et al., 2009	Germany	40	Department of Dermatology, Charité-Universitätsmedizin	0	40	52.3	29 months
Demir et al., 2013	Germany	21	NI	2	19	47, Range, 30 – 80	58 months
Grippaudo et al., 2014	Italy	26	NI	0	26	43, Range 28 -74	36 months
Harlim et al., 2018	Indonesia	31	NI	0	31	Range 20 – 52	NI
Kadouch et al., 2013	Netherlands	85	Department of Plastic and Reconstructive Surgery at Onze Lieve Vrouwe Gasthuis in Amsterdam	40	45	54, Range 27–79	42 months
Kadouch et al., 2014	Netherlands	32	Department of Plastic and Reconstructive Surgery at Onze Lieve Vrouwe Gasthuis in Amsterdam	16	16	55,4, Range 25 – 76	47.5 months
Lombardi et al., 2004	Switzerland	11	NI	0	11	55	NI
Uth et al., 2016	Denmark	37	Department of Dermatology, Herlev-Gentofte Hospital, and at the Department of Plastic Surgery, Breast Surgery, and Burns Treatment, Rigshospitalet	2	35	39, Range 19–69	24 months
Wiest et al., 2009	Germany	10	Klinikum Munchen-Schwabing, Department of Dermatology	0	10	Range 45 to 59	NI

NI, not informed.

Note: this table is not a part of the search process of the systematic review.

Supplementary Table 2. Search Strategies

PubMed	#1 = (“Oral foreign body granuloma” OR “granulomatous foreign body reactions” OR “giant cell foreign reactions” OR “granulomatous reaction” OR “foreign bodies” OR "Granuloma, Foreign-Body" OR "Giant Cells, Foreign-Body" OR "Foreign-Body Migration") #2 = (“hyaluronic acid” OR "orofacial dermal fillers” OR “silicone injection” OR “silicone” OR “cosmetic filler” OR “soft tissue filler” OR biomaterial OR “exogenous filler” OR "dermal fillers" OR "biocompatible materials") #3= ("mouth" OR "oral cavity" OR "cavitas oris" OR "oral cavity proper" OR "mouth cavity proper" OR "cavitas oris propria" OR perioral OR lip OR lips OR face) #1 AND #2 AND #3
Scopus	#1 = (“Oral foreign body granuloma” OR “granulomatous foreign body reactions” OR “giant cell foreign reactions” OR “granulomatous reaction” OR “foreign bodies” OR "Granuloma, Foreign-Body" OR "Giant Cells, Foreign-Body" OR "Foreign-Body Migration") #2 = (“hyaluronic acid” OR "orofacial dermal fillers” OR “silicone injection” OR “silicone” OR “cosmetic filler” OR “soft tissue filler” OR biomaterial OR “exogenous filler” OR "dermal fillers" OR "biocompatible materials") #3 = ("mouth" OR "oral cavity" OR "cavitas oris" OR "oral cavity proper" OR "mouth cavity proper" OR "cavitas oris propria" OR perioral OR lip OR lips OR face) #1 AND #2 AND #3
Embase	#1 = (“Oral foreign body granuloma” OR “granulomatous foreign body reactions” OR “giant cell foreign reactions” OR “granulomatous reaction” OR “foreign bodies” OR "Granuloma, Foreign-Body" OR "Giant Cells, Foreign-Body" OR "Foreign-Body Migration") #2 = (“hyaluronic acid” OR "orofacial dermal fillers” OR “silicone injection” OR “silicone” OR “cosmetic filler” OR “soft tissue filler” OR biomaterial OR “exogenous filler” OR "dermal fillers" OR "biocompatible materials") #3 = ("mouth" OR "oral cavity" OR "cavitas oris" OR "oral cavity proper" OR "mouth cavity proper" OR "cavitas oris propria" OR perioral OR lip OR lips OR face) #1 AND #2 AND #3
	Oral foreign body granuloma OR granulomatous foreign body reactions OR giant cell foreign

MedLine Ovid	reactions OR granulomatous reaction OR foreign bodies OR Granuloma, Foreign-Body OR Giant Cells, Foreign-Body OR Foreign-Body Migration) AND (hyaluronic acid OR orofacial dermal fillers OR silicone injection OR silicone OR cosmetic filler OR soft tissue filler OR biomaterial OR exogenous filler OR dermal fillers OR biocompatible materials) AND (mouth OR oral cavity OR cavitas oris OR oral cavity proper OR mouth cavity proper OR cavitas oris propria OR perioral OR lip OR lips OR face)
Web of Science	#1 = (“Oral foreign body granuloma” OR “granulomatous foreign body reactions” OR “giant cell foreign reactions” OR “granulomatous reaction” OR “foreign bodies” OR "Granuloma, Foreign-Body" OR "Giant Cells, Foreign-Body" OR "Foreign-Body Migration") #2 = (“hyaluronic acid” OR "orofacial dermal fillers” OR “silicone injection” OR “silicone” OR “cosmetic filler” OR “soft tissue filler” OR biomaterial OR “exogenous filler” OR "dermal fillers" OR "biocompatible materials") #3 = ("mouth" OR "oral cavity" OR "cavitas oris" OR "oral cavity proper" OR "mouth cavity proper" OR "cavitas oris propria" OR perioral OR lip OR lips OR face) #1 AND #2 AND #3
LILACS	(Tw:(“foreign bodies” OR "foreign bodies/" OR "foreign body" OR "foreign body giant cell" OR "foreign body giant cell/" OR "foreign body granuloma" OR "foreign body granuloma/" OR "foreign body migration" OR "foreign body migration/" OR "foreign body reaction" OR "foreign body reaction/")) AND (Tw: ("orofacial" OR "face" OR "lip" OR "mouth" OR "perioral" OR "perioral/" OR "periorbicular"))
Google Scholar	“Oral foreign body granuloma” OR “granulomatous foreign body reactions” OR “giant cell foreign reactions” OR “granulomatous reaction” OR “foreign bodies” OR "Granuloma, Foreign-Body" OR "Giant Cells, Foreign-Body" OR "Foreign-Body Migration" *filetype:pdf* AND “hyaluronic acid” OR "orofacial dermal fillers” OR “silicone injection” OR “silicone” OR “cosmetic filler” OR “soft tissue filler” OR biomaterial OR “exogenous filler” OR "dermal fillers" OR "biocompatible materials" *filetype:pdf* AND "mouth" OR "oral cavity" OR "cavitas oris" OR "oral cavity proper" OR "mouth cavity proper" OR "cavitas oris propria" OR perioral OR lip OR lips OR face *filetype:pdf*

OpenGrey	“Oral foreign body granuloma” OR “granulomatous foreign body reactions” OR “giant cell foreign reactions” OR “granulomatous reaction” OR “foreign bodies” OR "Granuloma, Foreign-Body" OR "Giant Cells, Foreign-Body" OR "Foreign-Body Migration" AND “hyaluronic acid” OR "orofacial dermal fillers” OR “silicone injection” OR “silicone” OR “cosmetic filler” OR “soft tissue filler” OR biomaterial OR “exogenous filler” OR "dermal fillers" OR "biocompatible materials" AND "mouth" OR "oral cavity" OR "cavitas oris" OR "oral cavity proper" OR "mouth cavity proper" OR "cavitas oris propria" OR perioral OR lip OR lips OR face *(Keyword: Dentistry)*

Supplementary Table 3. Articles excluded with their reasons

Author, Year	Reason for exclusion*
Abtahi-Naeini, B. et al., 2019	6
Alam, M. et al., 2007	6
Alijotas-Reig, J. et al., 2008	7
Alijotas-Reig, J. et al., 2009	7
Alijotas-Reig, J. et al., 2009	7
Al-Kutubi, H. et al., 2019	7
Amemiya, T. et al., 1994	6
Amin, S. P. et al., 2004	6
Andre, P. et al., 2008	3
Andreu-Barasoain, M. et al., 2013	7
Anwar, M. U. et al., 2007	6
Artzi, O. et al., 2016	7
Bachmann, F. et al., 2009	7
Bae, B. et al., 2016	3
Bakker, C. V et al., 2013	9
Bakkour, W. et al., 2016	7
Blanchard, J. et al., 2017	7
Brazelli, V et al., 2007	9
Bringel, D. M. et al., 2012	6
Brongo, S. et al., 2013	6
Bruges, M et al., 2011	7
Burgess, C. M. et al., 2008	3
Camacho, J. P. et al., 2018	4
Cameron, A. et al., 2020	8
Chae, S. Y. et al., 2015	7
Chang, C. S. et al., 2018	8
Choi, H. J. et al., 2014	6
Choi, S. Y. et al., 2016	7

Christensen, L. et al, 2005	6
Colombo, G. et al., 2010	5
Colombo, G. et al., 2011	6
Comez, A. T. et al., 2014	8
Croker, B. et al., 2018	7
Demir, E. et al., 2013	7
Di Meo, N. et al., 2020	7
Dolwick, M. F. et al., 1985	5
Duhovic, C. et. Al. , 2016	7
El-Khalawany, M. et al., 2015	4
Eun, Y. S. et al., 2014	7
Gandy, J. et al., 2017	6
Garey, R. C. et al., 1976	8
Goldman, A. et al., 2019	6
González, M. C. et al., 2013	7
Gosau, M. et al., 2008	1
Gouvêa, A. F. et al., 2011	8
Grass, J. et al., 2020	7
Green, J. et al., 2011	7
Grippaudo, F. R. et al., 2014	7
Hachach-Haram, N. et al., 2013	6
Hannon, S. M. et al., 1983	8
Harlim, A. et al., 2018	7
Hibler, B. P. et al, 2018	7
Highstein, M. J. et al., 2015	8
Horn, M. et al., 2008	5
Jansen, T et al. et al., 2013	9
Jones, D. H. et al., 2019	8
Jordan, D. R. et al., 2015	6
Juhász, M. L. et al., 2015	8
Kadouch, J. A. et al., 2013	7
Kadouch, J. A. et al., 2014	7
Kang J. D et al., 2004	9
Karfík, V.and Smahel, J., 1968	9
Kästner, S. et al., 2018	7
Kawakami, T. et al., 2007	9
Kehily, E. et al., 2015	6
Khoury, F. et al., 1984	9
Kim, K. J. et al., 2004	4
Kim, Y. J. et al., 2008	9
Kunjur, J. et al., 2013	6
Laglenne, E., 2004	9
Langer, C. et al., 2018	7
Lee, J. S. et al., 1995	9
Lee, M. J. et al., 2008	7

Lee, S. H. et al., 2017	8
Loda, G. et al., 2016	5
Lombardi, T. et al., 2004	7
Malik, S. et al., 2013	8
Mamelak, A. J. et al., 2009	7
Meigel, W. et al., 1989	9
Moulonguet, I. et al., 2013	6
Mukherji, S. et al., 2008	8
Nishida, M. et al., 2017	8
Nitzan, D. et al., 2004	9
Ocampo-Candiani, J. et al., 2008	6
Omranifard, M. et al., 2011	6
Orseth, M. L. et al., 2018	9
Ozturk, C. N. et al., 2013	7
Park, M. E. et al., 2016	4
Park, T. H. et al., 2011	5
Pónyai, K. et al., 2005	7
Poveda, R. et al., 2003	9
Poveda, R. et al., 2006	6
Pozuelo et al., 2020	7
Sa, H. S. et al., 2011	2
Salles, A. G. et al., 2008	7
Schanz, J. et al., 2012	8
Schuller-Petrovič, S. et al., 2013	4
Shim, W. H. et al., 2011	9
Sneistrup, C. et al., 2009	9
Souza, R. N. et al., 2016	5
Taufiq, S. et al., 2018	9
Tirakunwichcha, S. et al., 2003	7
Uchinuma, E. et al., 1997	8
Uth, C. C. et al., 2016	7
Vargas, A. F. et al., 2009	7
Wang, L. L. et al., 2018	5
Wiest, L. G. et al., 2009	7
Winer, L. H. et al., 1964	4
Zeltzer, A. A. et al., 2015	8
Zhao, Y. et al., 2004	9

***** 1 = Studies involving solid or semi-solid exogenous orofacial fillers; 2 = Studies involving autogenous filling; 3 = Studies that evaluate the quality of biomaterials; 4 = Foreign bodies outside the orofacial region; 5 = Surgical aesthetic procedures; 6 = Studies without clinical and/or histopathological analysis; 7 = Conference paper, conference abstract, letter, short survey, review, notes, commentary; 8 = Studies that not evaluate body reactions based on aesthetic procedures; 9 = Studies not found.

Supplementary Table 4. Histopathological features of cases of orofacial foreign body reactions identified in the systematic review

Author(s) (year of publication)	Material	Histological features
Akrish, S. et al., 2009	Bio-alcamid	Multiple foreign body–type granulomas composed of giant cells, epithelioid cells, and chronic inflammation, loose connective tissue matrix.
Akrish, S. et al., 2009	Bio-alcamid	Multiple foreign body–type granulomas composed of giant cells, epithelioid cells, and chronic inflammation within a loose connective tissue matrix
Rudolph, C. M. et al., 1999	Bioplastique	Nodular granulomatous infiltrate was embedded in a rather dense sclerotic stroma situated in the reticular dermis and adjacent subcutis, with extension into the upper muscle layer. The epidermis was lacking completely in both specimens. Numerous irregularly shaped, cystic structures distributed diffusely throughout the sclerotic stroma could be seen. Bizarrely shaped, translucent, nonbirefringent foreign bodies were observed within these irregularly formed cystic spaces that obviously represented retraction spaces due to formalin fixation and paraffin embedding. These cystic structures were almost completely outlined by multinucleate giant cells that sometimes protruded into the lumen, thus forming "arabesque" projections. In addition to these projections formed by giant cells, there were also intraluminal fibrous papillations. Occasionally, asteroid bodies were present in the cytoplasm of giant cells. The multinucleate giant cells themselves were surrounded by thickened collagen bundles intermingled with fibroblasts and a sparse infiltrate of lymphocytes with few eosinophils.
Rudolph, C. M. et al., 1999	Bioplastique	Nodular granulomatous infiltrate was embedded in a rather dense sclerotic stroma situated in the reticular dermis and adjacent subcutis, with extension into the upper muscle layer. The epidermis was lacking completely in both specimens. Numerous irregularly shaped, cystic structures distributed diffusely throughout the sclerotic stroma could be seen. Bizarrely shaped, translucent, nonbirefringent foreign bodies were observed within these irregularly formed cystic spaces that obviously represented retraction spaces due to formalin fixation and paraffin embedding. These cystic structures were almost completely outlined by multinucleate giant cells that sometimes protruded into the lumen, thus forming "arabesque" projections. In addition to these projections formed by giant cells, there were also intraluminal fibrous papillations. Occasionally, asteroid bodies were present in the cytoplasm of giant cells. The multinucleate giant cells themselves were surrounded by thickened collagen bundles intermingled with fibroblasts and a sparse infiltrate of lymphocytes with few eosinophils.
Heise, H. et al., 2001	Bovine collagen	Predominantly of lymphocytes and histiocytes. In one of the infiltrates giant cells and epitheloid cells were also present. Another infiltrate was located in the upper subcutis. It contained many eosinophils.
Jham, B. C. et al., 2009	Bovine collagen	Numerous cells with clear, often multiple, cytoplasmic vacuoles, displacing a single peripheral nucleus. A cytologic similarity to neoplastic lipoblasts raised the possibility of liposarcoma, especially in the case initially lacking a previous history of cosmetic treatment.
Philibert, F. et al., 2020	Bovine collagen	Presence of foreign-body granulomas developed in contact with spherical gaps of a size substantially identical to the Ellansé® vacuoles.
Poveda, R. et al., 2006	Bovine collagen	Discrete perivascular lymphoid infiltrates together with a focus of steatonecrosis and giant multinucleated cells of a type associated with a foreign body reaction.
Requena, C. et al., 2015	Bovine collagen	Deep dermis and hypodermis to be packed with clear spherical globules of different sizes with a mild granulomatous infiltrate composed of lymphocytes and histiocytes. The larger vacuoles were seen as extracellular deposits. Some of the foamy deposits were located between bands of striated muscle and the foreign material did not exhibit birefringence under polarized light microscopy.
Rolim, L. S. A. et al., 2019	Bovine collagen	Eosinophilic particles of irregular shapes which are surrounded by numerous multinucleated giant cells.
Toy, B. R. et al., 2003	Bovine collagen	Granulomatous inflammation with features of a mixed septal and lobular panniculitis. Stains for acid-fast bacilli, performed twice, revealed rare, positive-staining organisms. As a result, a second biopsy was performed to obtain fresh tissue for the identification of atypical mycobacteria using culture and polymerase chain reaction.
Daley et al., 2012	Calcium Hidroxiapatite	Intense granulomatous inflammation with epithelioid histiocytes and giant cells, associated with microspheric foreign bodies of unknown type, 20-50 m in diameter.
Daley et al., 2012	Calcium Hidroxiapatite	Identical microscopic appearances.

Daley et al., 2012	Calcium Hidroxiapatite	Identical microscopic appearances.
Rodrigues Carvalho, F. S. et al., 2018	Calcium Hidroxiapatite	Intense granulomatous inflammation with giant cells associated with microspheric foreign bodies showing a crackled appearance.
Rolim, L. S. A. et al., 2019	Calcium Hidroxiapatite	Amorphous particles of black staining, presence of multinucleated giant cells, moderate and focal inflammatory infiltrate.
Sankar, V. et al., 2007	Calcium Hidroxiapatite	Foreign material along with a florid foreign body giant cell reaction of the soft tissue, chronic inflammation and fibrosis. We also found evidence of chronic sclerosing sialadenitis.
Jham, B. C. et al., 2009	Foreign biopolymer	Nnumerous cells with clear, often multiple, cytoplasmic vacuoles, displacing a single peripheral nucleus. A cytologic similarity to neoplastic lipoblasts raised the possibility of liposarcoma, especially in the case initially lacking a previous history of cosmetic treatment.
Jham, B. C. et al., 2009	Foreign biopolymer	Numerous cells with clear, often multiple, cytoplasmic vacuoles, displacing a single peripheral nucleus. A cytologic similarity to neoplastic lipoblasts raised the possibility of liposarcoma, especially in the case initially lacking a previous history of cosmetic treatment.
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Jham, B. C. et al., 2009	Foreign biopolymer	Numerous cells with clear, often multiple, cytoplasmic vacuoles, displacing a single peripheral nucleus. A cytologic similarity to neoplastic lipoblasts raised the possibility of liposarcoma, especially in the case initially lacking a previous history of cosmetic treatment.
Alsaad, S. M., et al., 2012	Hyaluronic Acid	Granulomatous reaction in association with amorphous basophilic foreign material.
Alsaad, S. M., et al., 2012	Hyaluronic Acid	Granulomatous dermatitis in association with amorphous basophilic.
Anatelli, F. et al., 2010	Hyaluronic Acid	Acellular, basophilic material in the superficial, Solar elastosis and sparse lymphocytes were present in the dermis.
Bardazzi et al., 2007	Hyaluronic Acid	Paraffinoma with Swiss cheese appearance: a granulomatous reaction with fibrotic tissue containing fatty corpuscles and cysts delimitated by epithelial cells, foreign body giant cells and lymphocytes.
Cecchi, R. et al., 2014	Hyaluronic Acid	Vacuolated spaces surrounded by numerous histiocytes and chronic inflammation with numerous plasma cells and eosinophils.
Coughlin et al., 2020	Hyaluronic Acid	Epithelioid histiocytic and giant cell reaction of amorphous, nonpolarizable foreign material (0.5 cm) involving periparotid soft tissue and one benign intraparotid lymph node with histiocytic reaction also consistent with a foreign bodytype reaction.
Curi et al., 2015	Hyaluronic Acid	Granulomatous foreign body reaction related to the HA filler.
Davis et al., 2019	Hyaluronic Acid	Multinucleated giant cells and histiocytes closely associated with foreign material.
Descamps et al., 2008	Hyaluronic Acid	Foreign-body granuloma.
Edwards, P. C. et al., 2006	Hyaluronic Acid	Mucosa overlying connective tissue containing multiple vacuolated cyst-like areas. These cyst-like structures were surrounded by a granulomatous foreign body tissue reaction composed predominantly of histiocytes and foamy macrophages.

Esteves, A. L. et al., 2016	Hyaluronic Acid	Granulomatous reaction associated with hyaluronic acid, showing material surrounded by macrophages and multinucleated giant cells of the foreign body type.
Esteves, A. L. et al., 2016	Hyaluronic Acid	Granulomatous reaction associated with hyaluronic acid, showing the material surrounded by macrophages and multinucleated giant cells of the foreign body type.
Farahani, S. S. et al., 2012	Hyaluronic Acid	Pools of amorphous hematoxyphilic material surrounded by collagenized connective tissue and mature adipose tissue without inflammation or foreign body reaction.
Farahani, S. S. et al., 2012	Hyaluronic Acid	Amorphous hematoxyphilic material surrounded by densely collagenized connective tissue.
Farahani, S. S. et al., 2012	Hyaluronic Acid	Densely collagenized fibrovascular tissue covered by hyperkeratotic stratified squamous epithelium typical for a fibroma. Pools of basophilic and alcianophilic material, surrounded by thin septa of fibrous tissue and unassociated with inflammation or giant cell reaction.
Fernández-Aceñero, Ma J. et al., 2003	Hyaluronic Acid	Multinucleated foreign body giant cells.
Ghislanzoni, M. et al., 2006	Hyaluronic Acid	Dense multinodular infiltration involving the deep part of the dermis and the subcutaneous fat. Each nodule was found to be composed of several drops of a basophilic material showing a honeycomb aspect, surrounded by a layer of multinucleated giant cells with a dense peripheral infiltration of neutrophils and eosinophils.
Kaczorowski, M. et al., 2020	Hyaluronic Acid	Adipose tissue and fragments of skeletal muscle with numerous foreign body-type granulomas surrounded by dense fibrosis. Pools of amorphous greyish blue material in the center of each granuloma were surrounded by numerous multinucleated giant-cells with focal palisading and scattered mononuclear cells.
Maruyama, S. et al., 2017	Hyaluronic Acid	Skin necrosis throughout the entire epidermis, down to the midreticular layer of the dermis. Although inflammatory cell infiltration of the stroma was scarce, some inflammatory cells (eg, lymphocytes and neutrophils) were found in the perifollicular region.
Massone, C. et al., 2009	Hyaluronic Acid	Diffuse suppurative granulomatous reaction with presence of multinucleate giant cells and neutrophils involving the entire dermis. No areas of caseation were observed. Within the inflammatory reaction, 2 different exogenous materials were observed: filamentous, bluish-greyish structures with a bizarre configuration and multiple, bluish, spherical particles.
Mulinari-Brenner, F. et al., 2016	Hyaluronic Acid	Chronic granulomatous foreign body dermatitis occupying both superficial and deep dermis. No reaction center an HA-compatible amorphous material was observed.
Parulan, M. A. A. et al., 2019	Hyaluronic Acid	Amorphous, mucoid basophilic foreign material with surrounding rim of palisading epithelioid histiocytes and foreign-body giant cells, associated with infiltrates of lymphocytes and eosinophils.
Pézier, T. et al., 2014	Hyaluronic Acid	Granulomatous reaction with foreign body giant cells on a nonbirefringent gelatinous violet substance in direct smears stained with papanicolaou and cytoblocks stained with hematoxylin and eosin.
Pinheiro, M. V. et al., 2005	Hyaluronic Acid	Chronic granulomatous inflammatory process of tuberculoid and foreign body type with eosinophilia.
Requena, C. et al., 2001	Hyaluronic Acid	Nodular granulomatous infiltrate with numerous cystic structures dotted about within it was found. With higher magnification, polygonal, pink, translucent, nonbirefringent, extracellular foreign bodies were present within these cystic spaces, which represented retraction spaces as a result of shrinkage secondary to fixation. The granulomatous infiltrate was composed of epithelioid histiocytes, many multinucleate giant cells, and some lymphocytes. Abundant asteroid bodies were present in the cytoplasm of giant cells.
Requena, C. et al., 2015	Hyaluronic Acid	Diffuse interstitial vacuoles and cystic spaces of different sizes located between the dermal collagen bundles and in the hypodermis. The vacuoles were surrounded by some macrophages, several of which had foamy cytoplasm. Some of the foamy deposits were located between bands of striated muscle. The foreign material did not exhibit birefringence under polarized light microscopy.
Rolim, L. S. A. et al., 2019	Hyaluronic Acid	Amorphous particles of varying size of basophilic staining, permeated by multinucleated giant cells.
Rolim, L. S. A. et al., 2019	Hyaluronic Acid	Amorphous particles of varied size of basophilic staining sometimes more bluish, permeated by multinucleated giant cells.

Rongioletti, F. et al., 2015	Hyaluronic Acid	Granulomatous reaction surrounding round or ovals vacuoles of different size, giving the reaction the appearance of 'Swiss cheese' granuloma, consistent with siliconoma. In addition, the presence of irregularly shaped drops of amorphous basophilic Alcan blue positive material consistent with hyaluronic acid was more prominent adjacent to than inside the granulomatous reaction.
Rongioletti, F. et al., 2015	Hyaluronic Acid	Rounded vacuoles of similar shape and size that mimic normal adipocytes and that corresponds to implanted polymethylmethacrylate microspheres in a sclerotic stroma surrounded by an inflammatory reaction; many angular collections of amorphous basophilic material with homogeneous appearance; some deposits of a bluish material with filamentous and honeycomb appearance. While the first collection elicited an inflammatory granulomatous response, the two collections of bluish material with different shape were almost devoid of inflammatory reaction.
Sage, R. J. et al., 2009	Hyaluronic Acid	Dense inflammation in the dermis surrounding amorphous bluish gray material. The infiltrate was composed of foreign body giant cells, lymphocytes, and eosinophils.
Sage, R. J. et al., 2009	Hyaluronic Acid	Dense inflammation in the dermis surrounding amorphous bluish gray material. The infiltrate was composed of foreign body giant cells, lymphocytes, and eosinophils.
Shahrabi Farahani, S. et al., 2011	Hyaluronic Acid	Pools of amorphous hematoxyphilic material surrounded by collagenized connective tissue and mature adipose tissue without inflammation or foreign body reaction. Alcian blue and colloidal iron stains confirmed the presence of acid mucopolysaccharides such as HA.
Shahrabi Farahani, S. et al., 2011	Hyaluronic Acid	Pools of amorphous hematoxyphilic material surrounded by collagenized connective tissue and mature adipose tissue without inflammation or foreign body reaction. Alcian blue and colloidal iron stains confirmed the presence of acid mucopolysaccharides such as HA. salivary gland lobules were also noted and these exhibited very mild chronic obstructive sialadenitis.
Shahrabi Farahani, S. et al., 2011	Hyaluronic Acid	Pools of amorphous hematoxyphilic material surrounded by collagenized connective tissue and mature adipose tissue without inflammation or foreign body reaction. Alcian blue and colloidal iron stains confirmed the presence of acid mucopolysaccharides such as HA. a nodule of densely collagenized fibrovascular tissue covered by hyperkeratotic stratified squamous epithelium typical for a fibroma.
Sidwell, R. U. et al., 2004	Hyaluronic Acid	The external biopsy showed a florid chronic inflammatory infiltrate with a granulomatous reaction in the dermis. There were multiple fragments of refractile material surrounded by multinucleate foreign body-type giant cells. The internal biopsy showed squamous mucosa with a patchy mild chronic inflammatory infiltrate within the superficial stroma.
Vargas-Machuca, I. et al., 2006	Hyaluronic Acid	Dense and diffuse inflammatory infiltrate involving the deeper reticular dermis and extending to the subcutaneous tissue. The epidermis and superficial dermis were spared and the nodular inflammatory infiltrates were scattered by empty spaces. Higher magnification demonstrated foreign body granulomas surrounding translucent and irregular particles with polygonal shape and variable size.
Broly, M. et al., 2020	Hydroxyethylmethacrylate	Macrophagic and gigantocellular granulomas with optically empty-appearing polyedric vacuoles consistent with a delayed reaction to HEMA.
Weyand, B. et al., 2008	Hyaluronic Acid	Foreign bodies, asterisk, chronic inflammatory cells, number sign, foreign body major cells.
De bree et al., 2004	Polyacrylamide gel	Granulomas consisting of histiocytes, foreign body giant cells,fibroblasts, and lymphocytes surrounding amorphous material.
Karagozoglu, K. H. et al., 2008	Polyacrylamide gel	Salivary gland tissue with a histocytic inflammatory infiltrate containing numerous foreign body giant cells that were lining birefringent material.
Liu, H. L. et al., 2010	Polyacrylamide gel	Presence of amorphous basophilic foreign material deposits in the adipose tissue and skeletal muscle.
Liu, H. L. et al., 2010	Polyacrylamide gel	Infiltration of inflammatory cells into the dermis and subcutaneous fat.
Meyer, T. N. et al., 2016	Polyacrylamide gel	Amorphous basophilic material being engulfed by foreign body giant cells, forming granulomas amidst lympho-mono-hystiocytic inflammatory infiltrate, as well as some micro-abscesses in the dermis.

Rongioletti, F. et al., 2015	Polyacrylamide gel	Deep granulomatous giant cell reaction surrounding large collections of amorphous basophilic material, positive by Alcian blue stain, admixed and intermingled with vacuoles and cystic spaces of variable size.
Beer, K., 2009	Poly-L-Lactic acid	Extensive collagen production, with foreign body granulomas evident.
Beer, K., 2009	Poly-L-Lactic acid	Dense foreign body reaction with abundant formation of collagen.
Cox, S. E., 2009	Poly-L-Lactic acid	Foreign material with birefringent properties, surrounded by an inflammatory reaction including histiocytes.
Dijkema et al., 2005	Poly-L-Lactic acid	Foreign body giant-cell reaction with pseudo-encapsulation. Several histiocytic cells and giant cells containing poli - L- lactic were visible.
Dijkema et al., 2005	Poly-L-Lactic acid	Showed sarcoid-type granulomas with numerous foreign body giant cell formations deep into the dermis and subcutaneous tissues.
Feio, P. S. Q. et al., 2013	Poly-L-Lactic acid	Chronic inflammatory infiltrate in the connective tissue and the presence of numerous giant cells around translucent particles, showing fusiform or oval shapes.
Lin, C. H. et al., 2017	Poly-L-Lactic acid	Diffuse granulomatous inflammation throughout the deep dermis. The granulomatous inflammation was composed of foreign body giant cell reaction with macrophages, eosinophils, and neutrophils, and it was surrounded by at least two different extracellular materials.
Poveda, R. et al., 2006	Poly-L-Lactic acid	Chronic inflammatory infiltrate with eosinophiles and foreign body giant cells situated in the submucosa and fascicles of striated muscle.
Wildemore, J. K. et al., 2006	Poly-L-Lactic acid	Marked foreign-body giant-cell reaction with numerous fragments of polarizable foreign material, along with surrounding dermal fibrosis.
Alcântara, C. E. P et al., 2008	Polymethylmethacrylate	Amorphous crystalloid material, basophilic sometimes eosinophilic, intermingled to occa-sional multinucleated giant cells, mononuclearinflammatory cells, and a surrounding collagen fibers tissue.
Broly, M. et al., 2020	Polymethylmethacrylate	Histiocytic granulomatous reaction with giant cells surrounding optically round vacant vacuoles consistent with a delayed reaction to PMMA.
Cinotti, E. et al., 2015	Polymethylmethacrylate	Rounded vacuoles of homogeneous shape and size, surrounded by a diffuse granulomatous infiltrate.
da Costa Miguel et al., 2009	Polymethylmethacrylate	Several small round cystic spaces within the cytoplasm of large foreign body giant cells, or adjacent to giant cells containing asteroid bodies; The giant cells were randomly distributed against a background of fibrous connective tissue, and numerous lymphocytes and macrophages were observed.
Esteves, A. L. et al., 2016	Polymethylmethacrylate	Granulomatous reaction associated with the presence of homogeneous rounded spheres, compatible with polymethylmethacrylate, permeating the adjacent connective tissue.
Faria, K. M. et al., 2014	Polymethylmethacrylate	Multiple areas of negative microcystic-like spaces resembling adipocytes were found, limited by fibrous septa, along with focal areas of chronic inflammatory infiltrate with scarce giant cells within and around the spaces.
Fischer, J. et al., 2007	Polymethylmethacrylate	Dense sarcoidal granulomatous infiltrate at the dermal-subcutaneous fat border surrounding densely packed, small, round cystic spaces that contained translucent, nonbirefringent, uniformly sized microspheres.
Miguel, M. C. D. et al., 2009	Polymethylmethacrylate	Several small round cystic spaces within the cytoplasm of large foreign body giant cells, or adjacent to giant cells containing asteroid bodies. The giant cells were randomly distributed against a background of fibrous connective tissue, and numerous lymphocytes and macrophages were observed.
Quirino, M. R. D. S. et al., 2012	Polymethylmethacrylate	Multiple round spaces with similar sizes that were near to or within multinucleate giant cells. These giant cells were distributed among connective fibrous tissue with intense lymphocytic infiltrate and epithelioid macrophages. Upon lowering the condenser, round, sharply circumscribed, translucent, non-birefringent, foreign bodies were vaguely visible within the round spaces.

Requena, C. et al., 2001	Polymethylmethacrylate	Dense granulomatous infiltrate involving the reticular dermis. Higher magnification showed many round and apparently empty structures almost identical in size. After lowering the condenser, round, sharply circumscribed, translucent, nonbirefringent, extracellular foreign bodies surrounded by multinucleate giant cells, epithelioid histiocytes, and lymphocytes were detected.
Rolim, L. S. A. et al., 2019	Polymethylmethacrylate	Pseudocyst spaces of varying sizes permeated by multinucleated giant cells, forming lobes separated by septa of connective tissue.
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Rolim, L. S. A. et al., 2019	Polymethylmethacrylate	Pseudocyst spaces of varying sizes permeated by multinucleated giant cells, forming lobes separated by septa of connective tissue.
Rudolph, C. M. et al., 1999	Polymethylmethacrylate	Nodular and diffuse granulomatous infiltrate was present within the dermis, adjacent subcutaneous fat, and skeletal muscle. At scanning magnification, many round, apparently empty cystic structures almost identical in size and shape were observed, mimicking normal adipocytes. Closer inspection showed epithelioid cells and few multinucleate giant cells intermingled with a sparse lymphocytic infiltrate and occasional eosinophils, all of which surrounded the round vacuoles. The vacuoles presented singly and in small clusters embedded in a loose sclerotic stroma. Only after lowering of the condensor could round, sharply circumscribed, translucent, nonbirefringent foreign bodies-corresponding to the implanted polymethylmethacrylate pearls-be detected, and with difficulty, within the spaces.
Sidwell, R. U. et al., 2006	Polymethylmethacrylate	Granulomatous inflammatory reaction in the dermis with multinucleate giant cells. adjoining pink refractory material that did not show birefringence. In addition, smaller superficial and deep sarcoid-like epithelioid well-defined granulomas were visible.
Arin, M. J., et al., 2005	Silicone	Numerous ‘‘swiss cheese’’ like cystic spaces of varying sizes throughout all levels of the dermis compatible with silicone vacuoles, surrounded by granulomas composed of multinucleated giant cells and Langerhans cells that infiltrated into the muscle layer.
Baumann, L. S. et al., 2003	Silicone	Vacuolated spaces surrounded by numerous histiocytes and chronic inflammation with numerous plasma cells and eosinophils.
Bigatà, X. et al., 2001	Silicone	Numerous, large, clear vacuoles of varying sizes in the dermis surrounded by a lymphohistiocytic infiltrate.
Broly, M. et al., 2020	Silicone	Shaped and clear vacuoles, both extracellular and within giant cells or macrophages likened to “swiss cheese”.
Broly, M. et al., 2020	Silicone	Macrophage dermal granulomas in contact with optically empty vacuoles with development of fibrosis, consistent with a delayed granulomatous reaction to LIS.
Chen, Y. C. et al., 2011	Silicone	Foreign body granuloma variable-sized vacuoles in the fibrous dermis and subcutis; Numerous round to oval variable-sized vacuoles, surrounded by numerous lymphocytes, macrophages and giant cells with fibrous tissue formation.
Cho, S. et al., 2012	Silicone	Numerous round cavities of varying sizes with infiltrated histiocytes and giant cells and fibrosis.
Descamps et al., 2008	Silicone	Non-caseating granulomas with vacuolated macrophages that are characteristic of silicone granulomas.
Ellis, L. Z. et al., 2012	Silicone	Granulomatous process intercalated between and among the collagen bundles in the mid dermis.
Ellis, L. Z. et al., 2012	Silicone	Submucosal proliferation of histiocytes that nearly entirely replaced the submucosa. These histiocytes infiltrated around and between collagen bundles and surrounded neurovascular structures and adipocytes.
Ficarra, G. et al., 2002	Silicone	Skeletal muscle with surrounding connective tissue infiltrated by histiocytes and numerous cystic spaces. The cystic spaces varied somewhat in size and did not appear to contain residual droplets of silicone. Varying degrees of fibrosis were present among the cystic spaces.
Ficarra, G. et al., 2002	Silicone	Presence of silicone granuloma, and the histopathologic aspects were similar to those described in case 1.

Ficarra, G. et al., 2002	Silicone	Numerous empty small cystic spaces of varying sizes, surrounded by histiocytes, which diffusely infiltrated the superficial lamina propria down to underlying adipose tissue and striated muscle; The cystic spaces varied in size.
Ficarra, G. et al., 2002	Silicone	Diffuse granulomatous infiltrate with numerous multinucleated foreign body giant cells, many of which surrounded vacuoles of varying sizes containing small fragments of translucent refractile foreign material.
Ficarra, G. et al., 2002	Silicone	Extensive areas of fibrohistiocytic inflammation that surrounded numerous individual and empty cystic spaces of varying sizes, giving the appearance of Swiss cheese, extending from the interface with the overlying atrophic squamous epithelium to the superficial bundles of underlying skeletal muscle.
Ficarra, G. et al., 2002	Silicone	Vacuolated spaces surrounded by numerous histiocytes and chronic inflammation with numerous plasma cells and eosinophils.
Ficarra, G. et al., 2002	Silicone	Severe, incapacitating, and deforming rheumatoid arthritis, diagnosed 15 years previously.
Florin, W. et al., 2012	Silicone	Empty microvacuoles and cyst-like structures originally contained injected filler.
Gonçales, E. S. et al., 2009	Silicone	Numerous cells containing one or more clear vacuoles distorting the nucleus interspersed under. the epithelial layer, between and into striated muscle fibers, nerve bundles, and in blood vessel walls. These morphologic cellular features fulfill the requirement for immature lipoblasts. In addition, one fragment of amorphous and eosinophilic material without cells was microscopically observed adjacent to the soft tissue lesion.
Maly, A. et al., 2004	Silicone	Numerous cells with clear vacuoles in the cytoplasm, interspesed under the epthelial layer and between muscle fibers, displacing a single peripheral nucleus, as well as numerous bubbled vacuoles mimicking lipoblasts.
Mastruserio, D. N. et al., 1996	Silicone	Granulomatous process consistent with silicone granulomatous disease.
Mustacchio, V. et al., 2007	Silicone	Atrophic epidermis and a dermis occupied, through its entire thickness, by ‘cystic and macrophagic granulomas’ characterized by extracellular empty microcysts surrounded by a mainly mononuclear infiltrate of vacuolated macrophages. At low magnification, these microcysts appeared as round holes of different sizes, sometimes confluent, reminiscent of a ‘Swiss cheese pattern’. Giant cells were numerous, and they had a floret-like appearance with numerous clear, peripherally situated vacuoles and central closely packed nuclei. Mononuclear cells were also vacuolated with peripheral hyperchromatic notched signet-ring type nuclei, conferring a lipoblast-like appearance. Lymphocytes were scanty.
Pimentel, L. et al., 2002	Silicone	Inflammatory infiltrate composed of lymphocytes, histiocytes and foreign-body giant cells which surrounded empty cavities of different sizes giving it a ‘Swiss cheese’ appearance in the deep dermis and in the subcutaneous fat. Clear vacuoles were present in the cytoplasm of the giant cells (fig. 1) and macrophages that gave a foamy aspect to these cells.
Pimentel, L. et al., 2002	Silicone	Lesion compatible with a silicone-induced foreign body granuloma.
Pimentel, L. et al., 2002	Silicone	Silicone-induced foreign body reaction.
Pimentel, L. et al., 2002	Silicone	Silicone-induced foreign body reaction.
Rapaport, M. J. et al., 1996	Silicone	Showed typical silicone granulomatous response characterized by fibrous, foreign body giant cells engulfing silicone vacuoles, fixed tissue histiocytes, and lymphocytes.
Rapaport, M. J. et al., 1996	Silicone	Show typical vacuolization secondary to migrating silicone.
Rapaport, M. J. et al., 1996	Silicone	Accumulation of dense subcutaneous fibrotic masses distal to the scar indicative of local lymphatic obstruction wherever there is a surgical scar.

Requena, C. et al., 2001	Silicone	Dermal diffuse granulomatous infiltrate spattered with spherical clear globules of varying size. Closer inspection showed many multinucleate giant cells and histiocytes. replete with tiny vacuoles within their cytoplasm. The bigger vacuoles were extracellular. The material contained in the vacuoles was not birefringent under polarized light microscopy. A careful search for asteroid bodies was unsuccessful. The histopathologic findings were those of silicone granuloma.
Requena, C. et al., 2001	Silicone	The entire thickness of the dermis was involved by many round, sharply circumscribed, empty, nonbirefringent vacuoles of varying size embedded within thickened bundles of collagen and surrounded by a mild inflammatory infiltrate of lymphocytes and histiocytes. Some of the smaller vacuoles were seen inside the cytoplasm of histiocytes and multinucleated giant cells.
Requena, C. et al., 2015	Silicone	Mild deep dermal and hypodermal diffuse granulomatous infiltrate packed with spherical clear globules of different sizes. Some multinucleated giant cells and histiocytes with tiny vacuoles in the cytoplasm were observed. These larger vacuoles were seen as extracellular deposits. Some of the foamy deposits were located between bands of striated muscle.
Requena, C. et al., 2015	Silicone	Whole dermis to be filled with multiple round, empty, sharply circumscribed and non-birefringent vacuoles of varying sizes embedded within thickened bundles of collagen. This material was surrounded by a mild inflammatory infiltrate of lymphocytes and histiocytes. The smaller vacuoles were intracellular and the larger ones were extracellular.
Rubio-Flores, C. et al., 2005	Silicone	Localized diffuse infiltrate in the deep dermis, formed by macrophages loaded with round intracytoplasmic vacuoles of various sizes, which gave the tissue a characteristic foamy appearance.
Schmidt-Westhausen, A. M. et al., 2004	Silicone	Spherical homogeneous foreign body inclusions of 0.02–0.05 mm in diameter in fibrotic connective tissue. The inclusions were surrounded by moderate infiltration of lymphocytes in several areas indicating an inflammatory reaction. In addition, multinuclear giant cells were observed.
Serrano, T. L. et al., 2015	Silicone	Epithelioid-shaped macrophages surrounded by a rim of lymphocytes, filled with fibroblasts and collagen. multinucleated giant cells with haphazardly/peripherally nuclei shape, associated with areas without substance, indicating foreign body particles.
Wallace, J. R. et al., 1967	Silicone	Minor salivary gland in the submucosal soft tissues which, in part, showed a severe granulomatous inflammatory change with a mixed infiltrate. This suggests a possible foreign body-type granuloma reaction to some form of injectable material.
Waller, J. M. et al., 2008	Silicone	Pseudocystic spaces of varying sizes in the dermis and subcutis giving this biopsy a Swiss cheese appearance. Vacuoles of varying sizes and mixed infiltrate including foamy histiocytes and lymphocytes could be seen.
Wulu, J. A. et al., 2019	Silicone	Eyelid dermis was infiltrated by fatty like deposits and clear spaces focally surrounded by chronic inflammation consistent with granulomatous inflammation to “silicone oil leakage”.
Anastassov, G. E. et al., 2008	Vitamins	Clear spaces from the pre-existing silicone in the soft tissues as well as in the multinucleated foreign body type histiocytes and chronic inflammatory reaction.
Kamouna, B. et al., 2015	Vitamins	Dense inflammatory infiltrate involving the dermis and the hypodermis and numerous round ovoid cavities of varying sizes invading the whole dermis, resulting in a Swiss cheese-like appearance, consistent with a lipogranuloma.
Pascoaloti, M. I. M. et al., 2020	Silicone, Bovine collagen and PLA	Marked granulomatous inflammation permeating the lamina propria of the oral mucosa, the submucosa and the underlying skeletal striated muscle. The granulomas were primarily composed of macrophages, scarce epithelioid cells, foreign body multinucleated giant cells, and lymphocytes. Numerous small round cystic spaces, often containing a translucid sphere compatible with a PMMA microsphere, were observed in the cytoplasm of the foreign body multinucleated giant cells or near the giant cells. Fibroblasts and collagen fibers may also be seen at the periphery of the granulomas.
Reszko, A. E. et al., 2009	Silicone, collagen and PLA	Exuberant foreign body reaction with irregularly shaped polarizable crystals, consistent with PLA deposition, involving the mid and deep dermis. The giant cells were predominantly of a foreign body type and contained a number of vacuoles and crystalline material within the cytoplasm.

Supplementary Table 5. Critical appraisal of case reports.

Author/Year	*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?*
Akrish, S., et al., 2009	Yes	No	Yes	Yes	Yes	No	No	Yes
Alcântara, C. E. P., 2018	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Alsaad, S. M. et al., 2012	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Anastassov, G. E. et al., 2008	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Anatelli, F. et al., 2010	Yes	No	Yes	Yes	No	No	No	Yes
Arin, M. J. et al., 2005	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Bardazzi, F. et al., 2007	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Baumann, L. S., 2003	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Beer, K., 2009	Yes	No	Yes	Yes	Yes	No	No	Yes
Bigatà, X. et al., 2001	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Cecchi, R. et al., 2014	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Chen, Y. C. et al., 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cho, S. et al., 2012	Yes	No	Yes	Yes	Yes	No	No	No

Cinotti, E. et al., 2015	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Coughlin, A. et al., 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Curi, M. M. et al., 2015	Yes	No	Yes	Yes	Yes	No	No	Yes
da Costa Miguel, M. C. et al., 2009	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Davis, A. et al., 2019	Yes	Yes	Yes	Yes	No	No	No	Yes
De Bree, R. et al., 2004	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Descamps, V. et al., 2008	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Dijkema, S. J. et al., 2005	Yes	No	Yes	No	Yes	No	No	No
Edwards, P. C. et al., 2006	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Ellis, L. Z. et al., 2012	Yes	No	Yes	Yes	Yes	No	No	Yes
Faria, K. M. et al., 2014	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Feio, P. S. Q. et al., 2013	Yes	No	Yes	Yes	No	No	No	Yes
Fernández-Aceñero, Ma J. et al., 2003	Yes	No	Yes	Yes	No	No	No	No
Fischer, J. et al., 2007	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Florin, W. and Mandel, L., 2012	Yes	No	Yes	Yes	No	No	No	Yes
Ghislanzoni, M. et al., 2006	Yes	No	Yes	Yes	Yes	No	No	Yes
Gonçales, E. S. et al., 2009	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Heise, H. et al., 2001	Yes	No	Yes	No	Yes	No	No	Yes
Kaczorowski, M. et al., 2020	Yes	No	Yes	No	Yes	No	No	No
Kamouna, B.et al., 2015	Yes	No	Yes	Yes	Yes	No	No	No

Karagozoglu, K. H. and van der Waal, I., 2008	Yes	No	Yes	No	No	No	No	Yes
Lin, C. H. et al.., 2017	Yes	No	Yes	Yes	Yes	No	No	Yes
Liu, H.l. et al., 2010	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Maly, A. et al., 2004	Yes	Yes	Yes	Yes	Yes	No	No	No
Maruyama, S. et al., 2017	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Massone, C. et al., 2009	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Mastruserio, D. N. et al., 1996	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Meyer, T. N. et al., 2016	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Miguel, M. C. D. et al., 2009	Yes	No	Yes	Yes	Yes	No	No	Yes
Mulinari-Brenner, F. et al., 2016	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Mustacchio, V. et al., 2007	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Parulan, M. A. A. et al., 2019	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Pascoaloti, M. I. M. et al., 2020	Yes	Yes	Yes	Yes	No	Yes	No	yes
Pézier, T. et al., 2014	Yes	Yes	Yes	Yes	Yes	Yes	No	yes
Philibert, F. et al., 2020	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Pimentel, L. et al., 2002	Yes	Yes	Yes	Yes	No	No	No	No
Pinheiro, M. V. et al., 2005	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Quirino, M. R. D. S. et al., 2012	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Reszko, A. E. et al., 2009	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes

Rodrigues Carvalho, F. S. et al., 2018	Yes	No	Yes	Yes	Yes	No	No	yes
Rongioletti, F. et al., 2015	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Rubio-Flores, C. et al., 2005	Yes	No	Yes	Yes	Yes	No	No	Yes
Sage, R. J. et al., 2009	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Sankar, V. et al., 2007	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Schmidt-Westhausen, A. M. et al., 2004	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Serrano, T. L. et al., 2015	Yes	Yes	Yes	Yes	No	No	No	Yes
Shahrabi Farahani, S. et al., 2011	Yes	Yes	Yes	Yes	No	No	No	Yes
Sidwell, R. U. et al., 2004	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Sidwell, R. U. et al., 2006	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Toy, B. R. et al., 2003	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Vargas-Machuca, I. et al., 2006	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Wallace, J. R. et al., 1967	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Waller, J. M. et al., 2008	Yes	Yes	Yes	Yes	No	No	No	Yes
Weyand, B. et al., 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wildemore, J. K. et al., 2006	Yes	Yes	Yes	Yes	No	No	No	Yes
Wulu, J. A. et al., 2019	Yes	Yes	Yes	Yes	No	No	No	yes

Supplementary Table 6. Critical appraisal of case series.

Author/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?*
Broly, M. et al., 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Cox, S. E., 2009	No	No	No	Yes	Yes	Yes	Yes	No	Yes	No
Daley, T. et al., 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Esteves, A. L., 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Farahani, S. S. et al., 2012	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	No
Ficarra, G. et al., 2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Jham, B. C. et al., 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Poveda, R. et al., 2006	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	yes
Rapaport, M. J. et al., 1996	No	No	No	No	Yes	Yes	Yes	No	Yes	yes
Requena, C. et al., 2001	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No
Requena, C. et al.,	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No

2015										
Rolim, L. S. A. et al., 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Rudolph, C. M. et al., 1999	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	no

3 CONSIDERAÇÕES FINAIS

O presente artigo científico fornece evidências de como as reações de corpos estranhos se manifestam clinicamente e histologicamente nos indivíduos, definindo qual a predileção de sexo, idade, sintomatologia e duração das lesões, bem como quais foram os principais meios de tratamento, tipos de biópsia realizados, duração entre injeção e reação da lesão, recorrência, *follow-up* e diagnósticos diferenciais clínicos e histológicos discutidos dentre os casos clínicos incluídos na revisão sistemática. Baseado nos resultados encontrados e no período contemporâneo ao qual estamos vivendo em que a cada dia que passa, mais procedimentos estéticos na região orofacial são realizados, principalmente por cirurgiões dentistas, cabe a nós, também, sermos capazes de identificar as principais causas e consequências que essas lesões podem proporcionar bem como realizar o correto diagnóstico e tratamento para os pacientes que desenvolvem reações de corpos estranhos, uma vez que o cirurgião dentista é frequentemente o primeiro profissional a ser contatado pelo paciente para diagnóstico na região orofacial.

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ANEXO – REGISTRO PROTOCOLO PROSPERO - *International prospective register of systematic reviews*

NIHR National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Foreign body reactions related to orofacial cosmetic fillers: a systematic review.

Manoela Martins, Lucas Santos, Lauren Schuch, Felipe Silveira, Vivian Wagner

Citation

Manoela Martins, Lucas Santos, Lauren Schuch, Felipe Silveira, Vivian Wagner. Foreign body reactions related to orofacial cosmetic fillers: a systematic review.. PROSPERO 2020 CRD42020209942 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020209942

Review question

The purpose of this present study is to integrate the available clinical data regarding foreign body reactions related to cosmetic fillers in the orofacial region into a systematic review. In recent years, reports about the development of foreign body reactions in the orofacial region occurring after the infiltration of biomaterials are increasing.

Searches

Electronic searches without restriction of publication date or language will be performed in PubMed (National Library of Medicine), Web of Science (Thomson Reuters), Scopus (Elsevier), Embase (Elservier) and MEDLINE OVID . A combination of the Boolean operators AND/OR and the following terms will be used to identify pertinent studies: (“Oral foreign body granuloma” OR “granulomatous foreign body reactions” OR “giant cell foreign reactions” OR “granulomatous reaction” OR “foreign bodies” OR "Granuloma, ForeignBody" OR "Giant Cells, Foreign-Body" OR "Foreign-Body Migration") AND (“hyaluronic acid” OR "orofacial dermal fillers” OR “silicone injection” OR “silicone” OR “cosmetic filler” OR “soft tissue filler” OR biomaterial OR “exogenous filler” OR "dermal fillers" OR "biocompatible materials") AND ("mouth" OR "oral cavity" OR "cavitas oris" OR "oral cavity proper" OR "mouth cavity proper" OR "cavitas oris propria" OR perioral OR lip OR lips OR face).

Types of study to be included

It will be included case reports and case series. The following points will be collected from the included studies: (1) general characteristics from the included studies (author/year) (2) type of filler material (3) specific site of injection of the biomaterial; (4) clinical characteristics; (5) histopathological characteristics; (6) time between injection and reaction; (7) treatment and management of the lesion; and (8) follow-up / recurrence.

Condition or domain being studied

Nowadays, a variety of cosmetic materials has been used in the orofacial region for esthetic purposes. Nevertheless, severe long-term immunologic and inflammatory reactions may develop in the patients.

Participants/population

Individuals presenting granulomatous foreign body reaction related to cosmetic procedures in the orofacial region.

Intervention(s), exposure(s)

Application of cosmetic fillers in the orofacial region.

Comparator(s)/ control

Not applicable.

Main outcome(s)

The pre-specified primary outcomes will be the clinical and histopathological characteristics of the foreign body reactions related to cosmetic fillers in the orofacial region. In addition, the management and follow-up of the cases will be also evaluated.

Measures of effect

None.

Additional outcome(s)

None.

Measures of effect

None.

Data extraction (selection and coding)

Titles and abstracts of all studies will be reviewed by two authors. If the title and abstract met with the eligibility criteria, the study will be included. There will be no restriction on publication date or language. Animal, laboratory studies and opinion will be excluded. Possible disagreements between the two authors will be solved by a third one. 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 of the procedure; (5) clinical presentation; (6) reported symptoms and duration; (7) histopathological characteristics; (8) time between injection and reaction; (9) treatment; (10) recurrence; (11) types of dermal fillers used; (12) follow-up period; and (13) 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. 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.

Contact details for further information

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Organisational affiliation of the review

UFRGS

Review team members and their organisational affiliations

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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.

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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