J Biosci (2019) 44:78
DOI: 10.1007/s12038-019-9898-y

Analysis of nine cases of oral foreign body granuloma related to biomaterials

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MS received 16 September 2018; accepted 10 April 2019; published online 2 August 2019

Foreign bodies can penetrate the interior of soft and, sometimes, hard, tissues in various ways, including through open wounds, lacerations and traumatic accidents. However over the years, evidence of links between the use of dental materials and lately, significant involvement of aesthetic filler materials as foreign bodies in the oral and perioral region have been reported. Foreign body granulomas (FBGs) may develop from this exogenous material, histopathologically characterized by the presence of chronic inflammation and a high amount of macrophages. This study presents nine FBG cases affecting the oral and perioral regions, and carries out a literature review on the main clinical, histopathological and material characteristics used in dental and dermatological procedures related to the appearance of this type of granuloma.

Keywords. Cosmetic filler; endodontic filler; foreign body; foreign body granuloma

1. Introduction

Giant cells related to foreign bodies develop from the fusion of local macrophages that adhere to the surface of different synthetic materials, acting in their degradation. The insertion of foreign bodies into human oral and perioral tissues may originate from traumatic events, postoperative dental procedures (Jham *et al.* 2009; Rai *et al.* 2015) and dermatological aesthetic procedures (Jham *et al.* 2009; Lee *et al.* 2017). The origin of foreign body granulomas (FBGs) remains unclear, and their development is unpredictable, although their establishment has been associated with host response variability and infection (Costa Miguel *et al.* 2009), and may be related to pharmacological stimuli (Quirino *et al.* 2012). FBGs in periapical oral tissues may develop due to the insertion of exogenous material, either accidentally or through iatrogenic dental procedures (Plascencia *et al.* 2014). Over the years, an increase in the appearance of FBGs related to dermal filler cosmetic materials, such as bovine collagen in the 1980s used to treat wrinkles and soft-tissue defects, has been observed. Since then, many injectable materials have been developed in cosmetic dermatology to soften wrinkles, treat adipose tissue atrophy and promote increased soft face tissues, commonly injected into the dermis of perioral tissues, including the lips, nasolabial sulcus, cheeks (Requena *et al.* 2011), mentolabial groove, chin region and lip commissure (Bass 2015). Due to the variability of materials that can be inserted into tissues in different ways, careful anamnesis and clinical evaluations are necessary for accurate FBG diagnoses and appropriate treatment (Rai *et al.* 2015). In this context, this study reports nine FBG cases involving the oral cavity and perioral tissues, highlighting their clinical and histopathological characteristics and their relationship with different types of exogenous materials.

2. Materials and methods

The study protocol was approved by the Ethics Committee of the Federal University of Rio Grande do Norte (UFRN) (number 1.883.170). The inclusion criteria were all cases of

oral FBGs diagnosed between January 1969 and December 2016, selected for this study among 14,000 oral lesions diagnosed in the Oral Pathology Service files at UFRN. Data regarding patient age, sex, duration, location, symptomatology, clinical presentation, size, staining, use aesthetic filling substances, cases were compiled from the clinical data sent together with the biopsy records.

For histopathological analysis, all slides containing hematoxylin-eosin-stained 5-μm-thick sections were reassessed. Under light microscopy (Olympus CX31; Olympus Japan Co., Tokyo, JPN), oral FBGs were histologically reviewed by two previously trained examiners. Regarding histological findings, presence of giant cells, type of inflammatory infiltrates and identification of the biomaterial related to each case. The data were tabulated and analyzed by descriptive statistics using the IBM SPSS Statistics (version 20.0; IBM Corp., Armonk, NY, USA).

3. Results

The epidemiological and clinical data of our nine cases are summarized in table 1. Six cases were of female patients, three male patients, with mean age of 51.4 years for women and 39 years for men. With regard to FBG locations, five cases occurred in the lip region (two upper lip, two lower lip and one labial commissure. The lesion was presented in six cases (66.6%) as a fibrotic nodule, in three cases the duration ranged from 2 to 60 months and six cases were asymptomatic. The color of lesions was variable with a pale appearance in three cases. The use of filling material in aesthetic facial procedure was reported by four patients and only one patient reported recent dental treatment with endodontic procedure. In six cases, excisional biopsy was chosen, one case of incisional biopsy and in two cases there was no such information in the clinical file. Histopathology features of oral FBGs are in table 2. Several multinucleated giant cells (figure 1A) was seen in all cases, predominantly lymphocytic inflammatory infiltrates in all nine cases (100%), asteroid bodies (figure 1B) related to polymethylmethacrylate (PMMA) in three cases (33.3%) and vasculitis (figure 1C) in five cases (55.5%) were observed. Regarding the biomaterials related to our cases of oral FBGs, we found in four cases PMMA (44.4%), two cases hyaluronic acid (22.2%), in the remaining three cases calcium hydroxylapatite (11.1%), collagen hemostatic (11.1%) and nylon (11.1%).

4. Case reports

4.1 *Case 1*

During anamnesis, a 33-year-old female patient reported undergoing paraendodontic surgery, endodontic retreatment and calcium hydroxide ($Ca(OH)_2$) dressing 18 months prior

Table 1. Distribution of epidemiological and clinical aspects in nine cases of oral FBG

Case	Year	Age (years)/sex	Location	Clinical presentation	Size (cm)	Duration (months)	Symptomatology	Staining	Endodontic fillers	Dermal cosmetic fillers	Biopsy
1	2000	33/F	Posterior jaw	Cystic lesion	1.0	NA	NA	NA	Yes	No	NA
2	2006	59/F	Lip commissure	Fibrotic nodule	5.0	NA	Asymptomatic	Pale white	NA	NA	NA
3	2007	43/M	Posterior jaw	Soft lesion	NA	NA	Asymptomatic	Pale pink	NA	No	Excisional
4	2007	NA/F	Upper lip	Fibrotic nodule	4.0	NA	Asymptomatic	Pale red	No	Yes	Excisional
5	2009	54/F	Lower lip	Fibrotic nodule	1.0	48	Symptomatic	Yellow	No	Yes	Excisional
6	2009	14/M	Posterior jaw	Fibrotic nodule	10.0	12	Symptomatic	Pink	NA	No	Incisional
7	2011	56/F	Upper lip	Fibrotic nodule	2.0	60	Asymptomatic	Normal	No	Yes	Excisional excisional
8	2012	60/M	Lower lip	Fibrotic nodule	1.0	2	Asymptomatic	White	NA	NA	
9	2014	55/F	Buccal mucosa	NA	NA	NA	Asymptomatic	NA	No	Yes	Incisional

NA not available.

Table 2. Compatible material, category and histopathology features in nine cases of oral FBGs

Case	Compatible material	Category	Histopathology features
1	Calcium hydroxylapatite	Resorbable within years	Amorphous particles of black staining, presence of multinucleated giant cells, moderate and focal inflammatory infiltrate
2	PMMA microspheres	Permanent	Pseudocyst spaces of varying sizes permeated by multinucleated giant cells, forming lobes separated by septa of connective tissue
3	Collagen hemostatic	Resorbable within months	Eosinophilic particles of irregular shapes which are surrounded by numerous multinucleated giant cells
4	PMMA microspheres	Permanent	Pseudocyst spaces of varying sizes permeated by multinucleated giant cells, forming lobes separated by septa of connective tissue
5	PMMA microspheres	Permanent	Pseudocyst spaces of varying sizes permeated by multinucleated giant cells, forming lobes separated by septa of connective tissue
6	Hyaluronic acid	Resorbable within months	Amorphous particles of varying size of basophilic staining, permeated by multinucleated giant cells
7	PMMA microspheres	Permanent	Pseudocyst spaces of varying sizes permeated by multinucleated giant cells, forming lobes separated by septa of connective tissue
8	Suture material (Nylon)	Non-absorbable	Particles of varied morphology with crystalloid appearance, exhibiting grayish coloration and orange borders, circumscribed by an extensive area of inflammatory infiltrate
9	Hyaluronic acid	Resorbable within months	Amorphous particles of varied size of basophilic staining sometimes more bluish, permeated by multinucleated giant cells

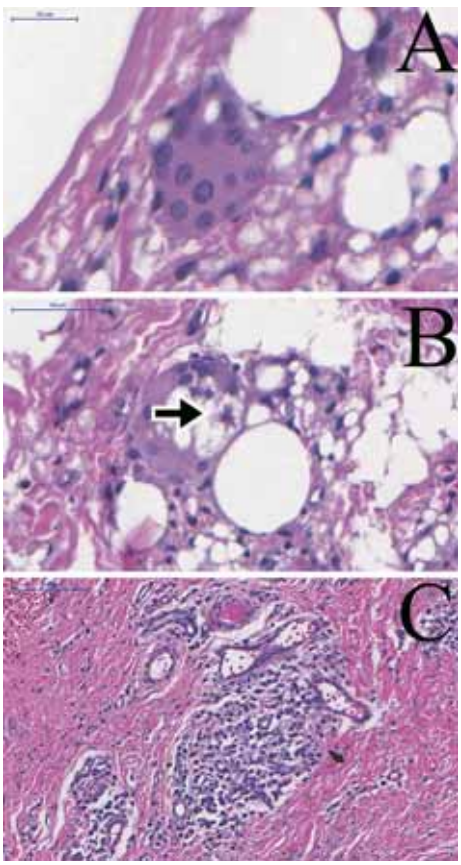

Figure 1. (**A**) Multinucleated giant cell (hematoxylin-eosin stain, Pannoramic viewer - 20 μm). (**B**) Asteroid body (arrow) in multinucleated giant cell (hematoxylin-eosin stain, Pannoramic viewer - 50 μm). (**C**) Vasculitis (hematoxylin-eosin stain, Pannoramic viewer - 100 μm).

to the exam. No noticeable changes were observed in an intraoral examination, with only a radiological indication of the presence of a circumscribed radiolucent lesion, measuring approximately 1 cm in diameter, related to the dental element 46. The diagnostic hypothesis of a radicular cyst was formulated. An excisional biopsy was performed and the samples were sent to the Pathology Sector of the Dentistry Department of the UFRN. A mononuclear inflammatory infiltrate of moderate intensity was observed in the focal during the histopathological analysis, with the presence of multinucleated giant cells around a blackened amorphous material, compatible, presenting a foreign body-type reaction (figure 2A) related to the identification of calcium hydroxyapatite deposits (table 2).

4.2 *Case 2*

The presence of a lesion with a consistent appearance, of sessile implantation and slow growth, measuring approximately 5 cm at a bilateral asymptomatic angle from the mouth, pale white, reported as developing over 10 months, was observed during an intraoral examination. A biopsy was carried out and the sample sent to our pathological anatomy service. The presence of different-sized pseudocystic spaces, compatible with PMMA microspheres, permeated by foreign body-type giant cells (table 2), and numerous different-sized macrophages and lymphocytes, distributed throughout the fibrous connective tissue forming septa, dividing the lesion into lobes (figure 2B) were observed.

4.3 *Case 3*

In 2007, a 43-year-old female patient attended a stomatology clinic and an intra-oral exam detected a pale and bleeding lesion presenting a rough appearance, with sessile implantation and slow growth, located in the buccal region

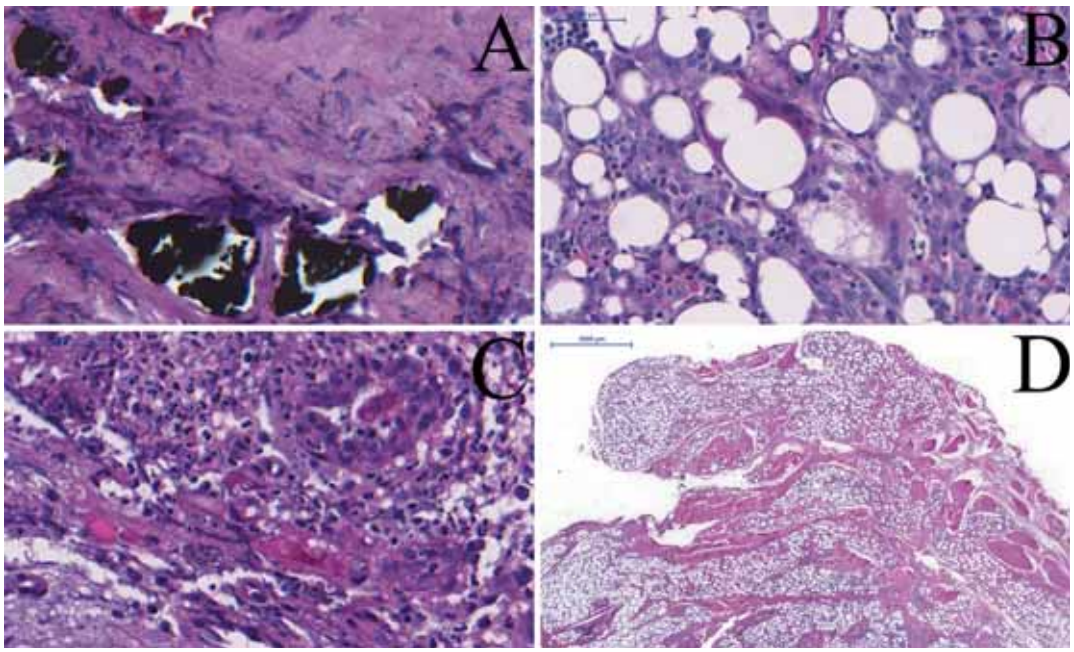

Figure 2. Photomicrographs showing oral FBGs. (**A**) Amorphous particles of black staining compatible with calcium hydroxylapatite (hematoxylin-eosin stain, Pannoramic viewer - 20 μm). (**B**) Pseudocyst spaces of varying sizes with a multinucleated giant cell with asteroid body (hematoxylin-eosin stain, Pannoramic viewer - 50 μm). (**C**) Eosinophilic particles of irregular shapes which are surrounded by numerous multinucleated giant cells, compatible with collagen hemostatic (hematoxylin-eosin stain, Pannoramic viewer - 50 μm). (**D**) Pseudocyst spaces of varying sizes compatible with PMMA, forming lobes separated by septa of connective tissue (hematoxylin-eosin stain, Pannoramic viewer - 1000 μm).

of teeth 44, 45 and 46. A radiographic examination revealed the presence of radiopaque areas, and the diagnosis hypothesis of pyogenic granuloma was formulated. An excisional biopsy was performed and the sample sent to our service. The presence of a foreign, irregular-shaped body (figure 2C) characterized by eosinophilic particles compatible with hemostatic collagen (table 2), surrounded by numerous multinucleated giant cells with variable nuclei size and number was evidenced by microscopy. This was surrounded by numerous multinucleated giant cells with varying nuclei size and amounts, characterized by both Langhans cells and foreign body-type cells, as well as intense, predominantly mononuclear, inflammatory infiltrates presenting numerous plasma cells and foamy macrophages.

4.4 *Case 4*

A female patient, also in 2007, attended a dental service to perform a clinical examination and, during anamnesis, reported the use of aesthetic material. The presence of an exophytic lesion of consistent aspect and sessile implantation in the upper lip was observed in an intra-oral examination. An excisional biopsy was performed and the specimen was sent to our anatomopathological service. The presence of microcystic spaces with similar diameters in a discrete lobular arrangement, separated by fibrous connective tissue septa, was microscopically observed. These spaces, compatible with PMMA microspheres, were present both in adjacent multinucleated foreign body-type giant cells (table 2) and as macrophages revealing a finely vacuolated material present in their cytoplasm (figure 2D).

4.5 *Case 5*

A 54-year-old female patient attended a dental care service in 2009 to perform a clinical examination. During anamnesis, the patient reported the use of an injectable substance of unknown nature on the lips for aesthetic purposes. A fibrous lesion of sessile implantation was evident, with an irregular aspect, measuring approximately 1 cm, located on the lower lip mucosa, reported as developing during 4 years. The diagnostic hypothesis was of a FBG, and the patient was submitted to an excisional biopsy. The presence of numerous negative round images (table 2) compatible with PMMA microspheres involving collagen fibers, predominantly mononuclear inflammatory cells and multinucleated giant cells (figure 3A) were verified microscopically.

4.6 *Case 6*

Also in 2009, a 14-year-old male patient with a biopsy history of osteoblastoma diagnosis in the mandible presented himself

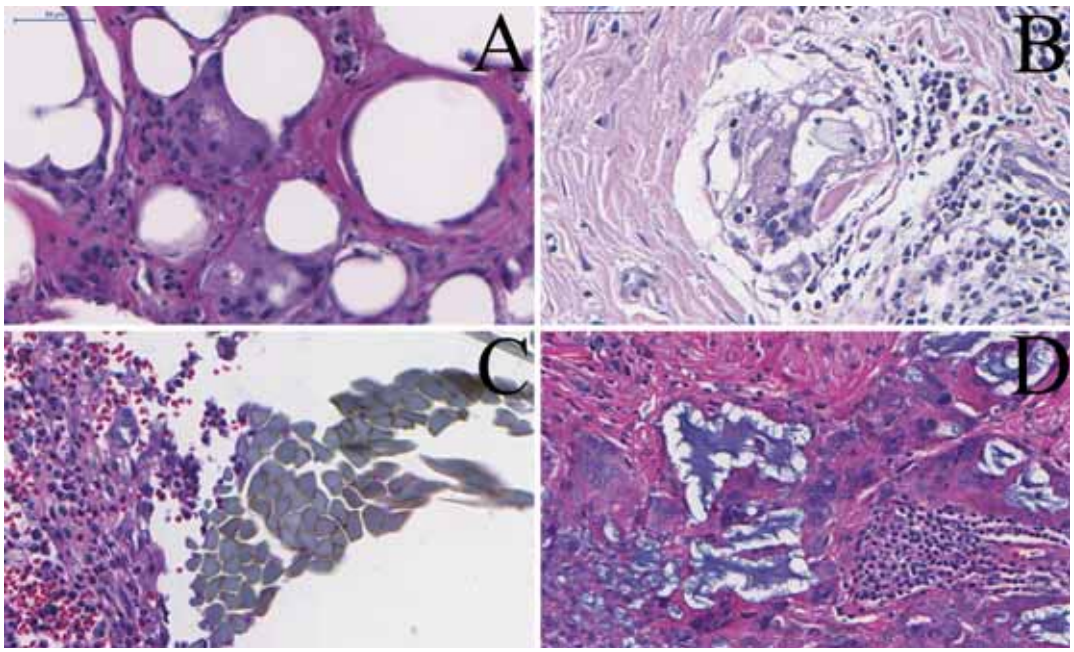

Figure 3. (**A**) Pseudocyst spaces of varying sizes permeated by multinucleated giant cells in oral FBGs (hematoxylin-eosin stain, Pannoramic viewer - 50 μm). (**B**) Amorphous particles of varying size of basophilic staining compatible with hyaluronic acid permeated by multinucleated giant cell (hematoxylin-eosin stain, Pannoramic viewer - 50 μm). (**C**) Particles of varied morphology with crystalloid appearance, exhibiting grayish coloration and orange borders, compatible with nylon (suture material) circumscribed by an extensive area of inflammatory infiltrate (hematoxylin-eosin stain, Pannoramic viewer - 50 μm). (**D**) Amorphous particles of varied size of basophilic staining sometimes more bluish, compatible with hyaluronic acid permeated by multinucleated giant cells (hematoxylin-eosin stain, Pannoramic viewer - 50 μm).

to our service and an intraosseous lesion located in the posterior region left jaw, exhibiting painful symptomatology, developing during one year, was noted. During a radiographic examination, the presence of a unilocular radiolucent lesion was observed in the posterior region of the mandible and the hypothesis of osteoblastoma recurrence was formulated. An incisional biopsy was performed and the sample sent to our anatomopathological service. The presence of amorphous foreign bodies compatible with hyaluronic acid (table 2), permeated by multinucleated foreign body-type giant cells and intense, predominantly mononuclear, inflammatory infiltrates (figure 3B) were evidenced by microscopy.

4.7 *Case 7*

In 2011, a 56-year-old female patient presenting an asymptomatic fibrous nodular lesion in the upper lip, reported as developing during 5 years, indicated previous removal of other similar lesions from the lower lip, diagnosed as FBGs. An excisional biopsy of the upper lip lesion with a diagnostic hypothesis of FBG was carried out and the sample sent to our service. The presence of numerous empty, different-sized, circular spaces, permeated by foreign body-type giant cells and with the presence of macrophages were observed through histopathological analyses. The exogenous material was compatible with PMMA microspheres, arranged in lobes separated by dense fibrous connective tissue septa (table 2).

4.8 *Case 8*

The presence of a nodular, fibrous lesion, measuring approximately 1 cm, located in the lower lip, reported as developing for 2 months, in a 60-year-old patient was observed in 2012, through an intra-oral examination performed at a dental care service. The diagnostic hypothesis was of cicatricial fibrosis, with the excised biopsy sample sent to our service. The presence of exogenous particles displaying varied morphology, sometimes elongated with a crystalloid appearance, grayish in color with orange borders, was observed during a histopathological examination, compatible with non-resorbable sutures (table 2), possibly nylon, circumscribed by an extensive inflammatory infiltrate area, predominantly composed of polymorphonuclear neutrophils, and also presenting some plasmocytes and lymphocytes (figure 3C).

4.9 *Case 9*

In 2014, a 55-year-old female patient attended a dental care service, reporting having completed an aesthetic filling in the

upper lip 2 years prior. A slow and asymptomatic growth lesion located in the jugal mucosa was evidenced in an intraoral examination. The hypothesis was of a non-specific chronic inflammatory process. A biopsy was performed and the sample sent to our service. The presence of numerous different-sized vacuoles, permeated by basophilic amorphous material, presenting blue areas compatible with hyaluronic acid (table 2), permeating the whole specimen, was evidenced by histopathology, as well as giant multinucleated cells dispersed throughout the sample and in proximity to the vacuoles. In other areas, the amorphous basophilic material was interspersed by bundles of skeletal muscle fibers, as well as a moderate mononuclear inflammatory infiltrates (figure 3D).

5. Discussion

FBG is a local tissue inflammatory response induced both by the trauma of biomaterial implantation and by its presence inside the body (Ye *et al.* 2010). Clinically, FBGs develop many months or years after the implantation of the foreign body and almost all at the same time. All FBG-involved areas show slight inflammation processes and nodules become noticeable. In the case of patients who underwent aesthetic procedures, such as filler injections, but, for some reason, omit this information, the differential diagnosis may vary due to the non-specific appearance of these granulomatous lesions. In this case, differential diagnoses may include glandular cheilitis, orofacial granulomatosis, sarcoidosis, Melkersson-Rosenthal syndrome, mucocele and soft-tissue neoplasia (Quirino *et al.* 2012). In this analysis, concerning lesion duration, four patients reported this information, presenting average FGB development of around 30.5 months, affecting six women and three men, with a mean age of approximately 47 years. Concerning clinical aspects, six cases (67%) presented a nodular appearance. This has been previously observed by Jham *et al.* (2009) in 100% of their evaluated cases, involving females, with mean age of 52.8 years.

Histopathologically, FBGs are constituted by the presence of numerous macrophages that act on exogenous material phagocytosis. During this process, macrophages exhibit an epithelial cell-like appearance and are referred to as epithelioid cells. Several multinucleated giant cells resulting from the fusion of these macrophages are scattered within this epithelioid mass, which is circumscribed by inflammatory infiltrates, predominantly composed of lymphocytes. These cell types in turn, produce cytokines that act on macrophage activation (Florin and Mandel 2012). Another histopathological finding related to some FBG cases is the presence of asteroid bodies (Shahrabi-Farahani *et al.* 2014; El-Khalawany *et al.* 2015). In this study, the presence of several multinucleated giant cells, predominantly lymphocytic inflammatory infiltrates in all nine cases, asteroid bodies related to PMMA in three cases and vasculitis were observed in five cases.

FBGs can be inserted into the oral cavity in different ways, such as by intentionally introducing objects into the mouth, compacting food into teeth presenting a necrotic pulp, leading to destruction of the pulp chamber, accidental displacement of a foreign body during dental procedures (Plascencia *et al.* 2014), i.e., the insertion of restorative and endodontic materials at the dental apex, as well as fragments of dental instruments and dental impression material (Genno and Assaf 2014). In addition, traumatic implantation, for example, due to car accidents may also lead to FBG insertion, such as glass fragments (Mazinis *et al.* 2005), and an unusual implantation of a bee sting in a patient's jugal mucosa has also been reported, leading to the formation of a FBG (Yamamoto *et al.* 2017).

Dental restorative materials used in prophylaxis that may be found in the oral cavity, mainly in gingival tissues, originating FBGs, include amalgam residue deposits (Koppang *et al.* 2007), resin fragments, glass ionomers (Consolaro and Bittencourt 2014) and abrasive compatible materials, the most common of the afore-mentioned materials (Koppang *et al.* 2007). None of the cases analyzed herein presented evidence of such restorative or prophylaxis materials.

Other materials may be related to the appearance of oral cavity FBG, such as those used in endodontic treatments. For example, the most commonly used root canal filling material is a $CaOH_2$ paste, administered through a pressure system using a syringe (Shahravan *et al.* 2012), which may occasionally leak out, depositing itself in the periodontal ligament and accumulating macrophages due to a non-specific inflammatory reaction, forming a granuloma but not establishing an immune response. For this reason this type of granuloma is known as foreign or non-immunogenic body granuloma type, and, as it is located in the periapical region of the tooth, it receives the denomination of a periapical FBG type (Consolaro and Bittencourt 2014). In this study, FBG originated from the presence of $Ca(OH)_2$-based endodontic filler material in only one case.

Regarding the use of elastomeric printing materials in the dental practice, polysulfide rubber, polyether, reversible hydrocolloid, silicone polysiloxane and vinyl rubber-based materials are routinely used in prosthetic procedures, usually without adverse consequences. However, pain and swelling after their use, allergies, localized inflammation, bone loss and the appearance of FBG due to retained imprinting material have been reported (Genno and Assaf 2014). No elastomeric printing materials were reported in this study.

In recent years, concern about aesthetics and signs of facial aging have gained importance and consequently, the use of fillers in the orofacial region has become more frequent. It is becoming increasingly common for many dermatologists and plastic surgeons to treat patients with soft-tissue augmentation and wrinkle treatment, applying different techniques (Alcântara *et al.* 2017). These include filler injections. The ideal filling agent should have a lasting

effect, offer good esthetic results, and be safe, biocompatible and stable at the application site, with minimal complications and no risk of migration (Requena *et al.* 2011).

Cosmetic dermal filler materials can be classified as reabsorbable/biodegradable, such as collagen and hyaluronic acid, or permanent/non-biodegradable as silicone and polymethacrylate (Chiang *et al.* 2017). These cutaneous cosmetic materials can also be categorized as fillers, biostimulators or combined, taking into account the area to be filled or the stimulatory effects observed in the dermal microenvironment. Hyaluronic acid, collagen, polyacrylamide and silicone oil gels display filling properties, while other materials can be used both for their filling properties and as biostimulators such as calcium hydroxyapatite and poly-L-lactic acid (PLLA) (Shahrabi-Farahani *et al.* 2014).

In general, complications related to dermal filler materials are related to two factors: the injection technique and the chemical composition of the product itself. Edema, erythema, ecchymosis, infections, migration of the filling agent and vascular involvement (arterial occlusion, tissue necrosis) are related to the applied technique. Complications such as allergies, hypersensitivity reactions, skin discoloration, formation of inflammatory nodules and granulomatous reactions (FBG) are related to the applied product (El-Khalawany *et al.* 2015; Chiang *et al.* 2017).

Oral FBG may also be related to the use of aesthetic filling substances in the orofacial region (Edwards *et al.* 2006; Junkins-Hopkins 2010; Grippaudo *et al.* 2014). This relationship has increased due to the popularization of these substances and, because patients are not aware of the relationship between oral granulomatous lesions (FBG) and their previous aesthetic procedures, they often omit information about the use of fillers, making the diagnosis of these lesions more complex (Quirino *et al.* 2012). Their use may, in some cases, compromise dental elements, as described by Marusza *et al.* (2012). Foreign body reactions after aesthetic facial procedures are more frequent in the nasolabial sulcus, labial commissure and lips, frequently related to the use of silicone, hyaluronic acid, collagen and PLLA (Pontes *et al.* 2012). In this study, only four patients reported undergoing an aesthetic procedure prior to the appearance of FBG. In these cases, the use of hyaluronic acid in one case and PMMA in three cases was verified. Another PMMA case where the patient did not report previous anesthesia procedures was identified through histopathological analyses.

After analyzing the reported cases, it is concluded that FBGs in oral tissues may be related to exogenous materials, used both in dental and dermatological procedures, with a predominance of the use of dermatological fillers, thus, mostly affecting women. This study also contributes to further histopathological evidence of FBGs, with the identification of asteroid bodies, as well as identification of the materials responsible for the appearance of these lesions, with PMMA as the most prevalent.

Compliance with ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the UFRN Research Ethics Committee, Natal, Brazil (number 1.883.170).

Informed consent Informed consent was obtained from all individual participants included in the study.

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Corresponding editor: Rita Mulherkar