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RESEARCH

Adverse Reactions Associated with Dermal Fillers in the Oral and Maxillofacial Region: A Venezuelan Experience

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Abstract

Background Dermal facial fillers are increasingly popular. Published reports on the clinical and histopathologic characteristics related to adverse reactions to dermal fillers in the facial region have been relatively well documented. This study adds to the literature on adverse reactions to injected filler in the oral and maxillofacial region in a South American population.

Methods A retrospective, descriptive cross-sectional study (2019–2020) was performed. The study population was a dermatology service in Venezuela. Clinical and histopathologic features of patients with adverse effects were documented.

Results A total of 35 cases of adverse reactions associated with cosmetic filler procedures were diagnosed during the analyzed period; of these, six cases (17.1%) involved the oral and maxillofacial region. All cases occurred in women. The mean age at diagnosis was 59.3 years (58–73). In three cases, dermal fillers were used in different locations on the face, while three involved the lips. Five patients exhibited adverse reactions to lip filler. All six cases were histopathologically diagnosed as foreign body reactions to injected material. Four and two cases revealed microscopic features compatible with hyaluronic acid and polymethylmethacrylate, respectively.

Conclusion Reflecting the dramatic increase in cosmetic procedures with soft tissue fillers, this study contributed by reporting six cases of foreign body reaction involving the oral and maxillofacial region, confirmed with biopsy and histopathology.

Keywords Biocompatible materials · Dermal fillers · Esthetic · Foreign body reaction

Introduction

Aging alters the pathophysiology of the skin, particularly the dermal collagen, resulting in a decrease in skin thickness and elasticity [1, 2]. The number of non-surgical facial cosmetic procedures performed worldwide has increased over the years, and different healthcare professionals including dentists, biomedical scientists and pharmacists, and estheticians, in addition to dermatologists and other physicians, perform these procedures [1, 2]. The injection of cosmetic fillers in the oral and perioral region has been used to soften wrinkles and rhytids and for facial sculpting [3, 4]. These materials can be classified into biological and non-biological, or according to their biodegradability, i.e., biodegradable and non-biodegradable [3, 4].

Although dermal fillers are generally considered safe, they have the capacity to produce adverse reactions and serious complications [1–4]. Some documented examples are erythema, ecchymosis, infection, hypersensitivity reactions,

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foreign body reactions, blood vessel occlusion, local tissue necrosis, seroma formation, nerve damage causing sensory or motor deficits, scarring, deep vein thrombosis, and pulmonary embolism [1–4]. The true incidence of filler complications is difficult to establish due to the lack of a universal reporting system. According to Chiang et al. [2], the incidence of these complications ranges from 0.02 to 2.8%. Most of these complications are transient; however, adverse reactions can permanently compromise the esthetic appearance and function of adjacent tissues [2, 5]. Moreover, the time elapsed from the intervention to the adverse reaction can vary from minutes to years after the filling procedure [1, 2].

In the oral and maxillofacial region, granulomatous foreign body reactions are the most common complications related to dermal fillers [1, 2, 5–7]. However, their diagnosis challenges clinicians, mainly because a detailed history of the injection of cosmetic fillers in such a region can be neglected by patients [6–8]. More recently, a systematic review identified that 23.6% of reports of foreign body reactions related to orofacial esthetic fillers came from Latin America; despite this, studies from Venezuela are very scarce [7]. Therefore, the purpose of the present study was to report the clinicopathological features of individuals with adverse reactions associated with dermal fillers in the oral and maxillofacial region diagnosed in a Venezuelan dermatological service.

Materials and Methods

Study Design and Ethical Clearance

This was a retrospective and cross-sectional study based on the medical records of the dermatology service at the Dr. José María Vargas Hospital, Caracas, Venezuela. The sample of this study consisted of patients diagnosed with adverse reactions associated with cosmetic filler materials in the oral and maxillofacial region between January 2019 and February 2020. The guidelines for strengthening the reporting of observational studies in epidemiology were followed [9]. The study was approved by the Institutional Ethics Committee (No. CB-062-2018) and the patient's identity remained anonymous according to the declaration of Helsinki.

Patients and Data Collection

All patients with an adverse event related to the use of injected dermal filler material in the oral/perioral region were included in the study. Individuals who reported immunological or other systemic diseases, those with previous adverse reactions in the same area before the esthetic procedure, or those who used cosmetic dermal filler material at an anatomical site other than the oral and maxillofacial region were excluded.

The following clinical data were collected: sex, age, presence and type of systemic disease, type and amount of filling material, type of professional who performed the esthetic procedure, anatomic site where the material was injected, period of time between the esthetic procedure and the development of the adverse reaction, as well as symptomatology and clinical aspects of the oral/perioral adverse reactions (e.g., swelling, infection, mucosal hyperpigmentation, and/or necrosis). Histopathology was also reviewed.

Diagnostic Rendering

Patients with adverse oral/perioral mucosal reactions underwent a biopsy under local infiltrative anesthesia. The samples were fixed in 10% formaldehyde and sent for histopathological examination. The biopsied cases were evaluated microscopically by routine staining (hematoxylin and eosin) under a light microscope (Olympus CX31, Olympus Japan Co., Tokyo, Japan). Morphological features including basophilic material at different levels of the dermis surrounded by histiocytes and multinucleated giant cells correspond to hyaluronic acid, while granulomatous infiltrate surrounding rounded vacuoles of similar shape and size that mimic normal adipocytes are compatible with polymethylmethacrylate [10, 11].

Data Analysis

Descriptive and quantitative data analysis was performed using the statistical package for the social sciences (SPSS) software, version 25.0 (SPSS Inc., Armonk, NY, USA).

Results

Clinical Aspects

A total of 35 cases of adverse reactions associated with injection of filler of cosmetic procedures were diagnosed during the analyzed period; of these, six (17.1%) involved the oral and maxillofacial region. Table 1 summarizes the patients clinical information. All cases occurred in female patients ($n=6$; 100%) with a mean age of 59.3 ± 10.5 years. None of the patients had systemic diseases.

Regarding esthetic procedures and characteristics of dermal fillers, 66.7% ($n=4$) of the procedures were performed by estheticians, and none of the patients knew which type of filler was used. Three (50%) procedures were performed exclusively on the lips, while in the other three cases the filling was performed at multiple locations on the face, such as the chin and eyelid; however, no adverse reactions occurred at these

Table 1 Data from patients diagnosed with adverse reactions to dermal filler materials in the oral and maxillofacial region

Case	Sex/age	Systemic disease	Professionals who applied dermal filler materials	Site of applications	Time elapsed between injection and reaction	Adverse reaction location	Histopathological diagnosis	Suspected dermal filler
1	F/60	Absent	Esthetician	Lips	1–12 months	Lips	Foreign body reaction	Polymethylmethacrylate
2	F/73	Absent	Esthetician	Lips	1–12 months	Lips	Foreign body reaction	Polymethylmethacrylate
3	F/41	Absent	Esthetician	Multiple sites on the face	≤ 1 month	Lips	Foreign body reaction	Hyaluronic acid
4	F/59	Absent	Plastic surgeon	Multiple sites on the face	1–12 months	Lips	Foreign body reaction	Hyaluronic acid
5	F/65	Absent	Plastic surgeon	Lips	1–12 months	Lower lip	Foreign body reaction	Hyaluronic acid
6	F/58	Absent	Esthetician	Multiple sites on the face	≥ 12 months	Buccal mucosa	Foreign body reaction	Hyaluronic acid

F female

latter sites. In one case, the adverse reaction started to develop between the first and second week after the cosmetic procedure. Two patients experienced adverse reactions between one and six months, two between one and 12 months, and one after one year.

Five patients (83.3%) exhibited clinically adverse reactions on the lips and one (16.7%) on the buccal mucosa. Of the cases involving the lips, four had swelling in both lips (Fig. 1A–D), while one had swelling in the lower lip with areas of hematoma (Fig. 1E). The lesion involving the buccal mucosa was a nodule with a smooth surface and fibrous consistency.

Morphological Data

All six cases were histopathologically diagnosed as foreign body reactions (Fig. 2). Dermal filler materials were identified according to the histopathological features observed under a light microscope. Two cases (33.3%) revealed uniform vacuoles, with a homogenous shape and different sizes, compatible with a polymethylmethacrylate substance. These vacuoles were surrounded by numerous foamy histiocytes/macrophages and formed lobules separated by septa of connective tissue (Fig. 2A–D). In four cases (66.7%), the histological pattern of the material was compatible with hyaluronic acid. This dermal filler material was characterized by the presence of a basophilic, amorphous, and acellular material surrounded by numerous foamy histiocytes/macrophages and multinucleated giant cells (Fig. 2E–F).

Discussion

According to the 2021 International Survey of the Society of Aesthetic Plastic Surgery, the demand for non-surgical procedures increased by 19.9% between 2020 and 2021 [12]. The United States and Brazil are the countries with the highest number of procedures, but other countries in Asia and South America also perform a significant number of non-surgical cases [12, 13]. We analyzed cases of adverse reactions associated with dermal fillers in the oral and maxillofacial region observed within a Venezuelan dermatological service. Similar to recent systematic reviews [1, 7], our data confirm that cases of foreign body reactions usually occur in middle-aged women, with the lips and buccal mucosa being the most affected sites [7]. The affected population is not surprising given that 86.8% of non-surgical cosmetic procedures are performed on female patients [12].

The eyelids and lips are the facial anatomical structures most targeted by anti-aging esthetic treatments [7, 14]. In the present study, 50% of the procedures were performed exclusively on the lips and 83.3% of the cases of adverse reaction occurred at this anatomical site. The lesions on the lips exhibited a clinical appearance of nodular or diffuse swelling, consistent with prior reports such as that by Santos et al. [7]. The differential diagnosis of swelling and nodules of the lips, however, is broad, and includes

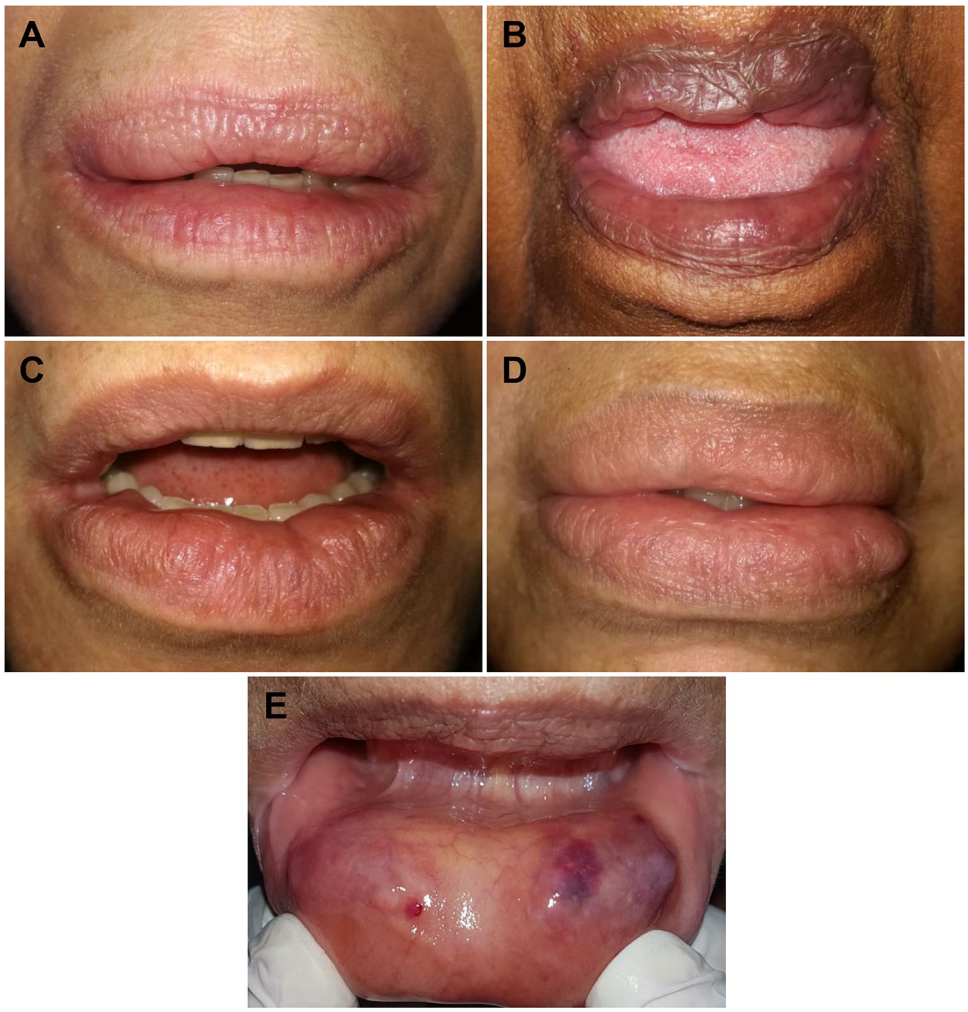

Fig. 1 Clinical aspect of adverse reactions to dermal fillers in the oral and maxillofacial region. **A–D** Cases 1–4: asymptomatic and normal-colored fibrous submucosal nodules located in the upper and lower lips. **E** Case 5: painless bilateral nodules in the mucosa of the lower lip associated with marked redness

traumatic, reactive/inflammatory and neoplastic causes [3, 7, 15]. It is noteworthy that chronic macrocheilia, an inflammatory condition responsible for swelling of one or both lips, involves miscellaneous etiological diagnoses, such as leishmaniasis, Miescher's granulomatous cheilitis, Melkersson–Rosenthal syndrome, Crohn's disease, sarcoidosis, leprosy, and tuberculosis [16]. However, the time of evolution of these last conditions, i.e., at least eight weeks [16], is similar to that observed in individuals with iatrogenic macrocheilia related to foreign body granulomas, which may appear a few days or years after injections of cosmetic fillers [1, 7], as also observed in the present study.

It is known that non-surgical esthetic procedures are growing exponentially due to the use of dermal filler materials with properties related to high biocompatibility, implantation stability, longevity, and low complications in the short and long term [4, 6]. About 12 different types of dermal fillers related to foreign body reactions in the oral and maxillofacial region have been reported [7]. Hyaluronic acid is the most used and highly recommended dermal filler for esthetic procedures in the lips and perioral region, as it is non-permanent and provides hydration, volume, and structural support to the tissues [4, 6, 7, 13, 17]. Silicone, in its liquid and gel forms, is also a widely used substance for the cosmetic correction of small wrinkles or scars of the face and volume augmentation of soft tissues [18]. Polymethylmethacrylate, on the other hand, is a rigid permanent filler composed of microspheres with the potential for long-lasting results [4, 17, 19]. Even though the patients were unable to inform which type of dermal filler was used in the procedures, based on the microscopic findings, we suspected that the substances used were hyaluronic acid and polymethylmethacrylate.

Histopathologically, the foreign body reaction is characterized by the presence of numerous macrophages and multinucleated giant cells that promote the phagocytosis of exogenous material. In fact, the histological features depended on the type of the filler material used [3, 7]. As observed in four cases of the current study, foreign body reactions were associated with hyaluronic acid. Such substances have been described as deposits of amorphous basophilic material

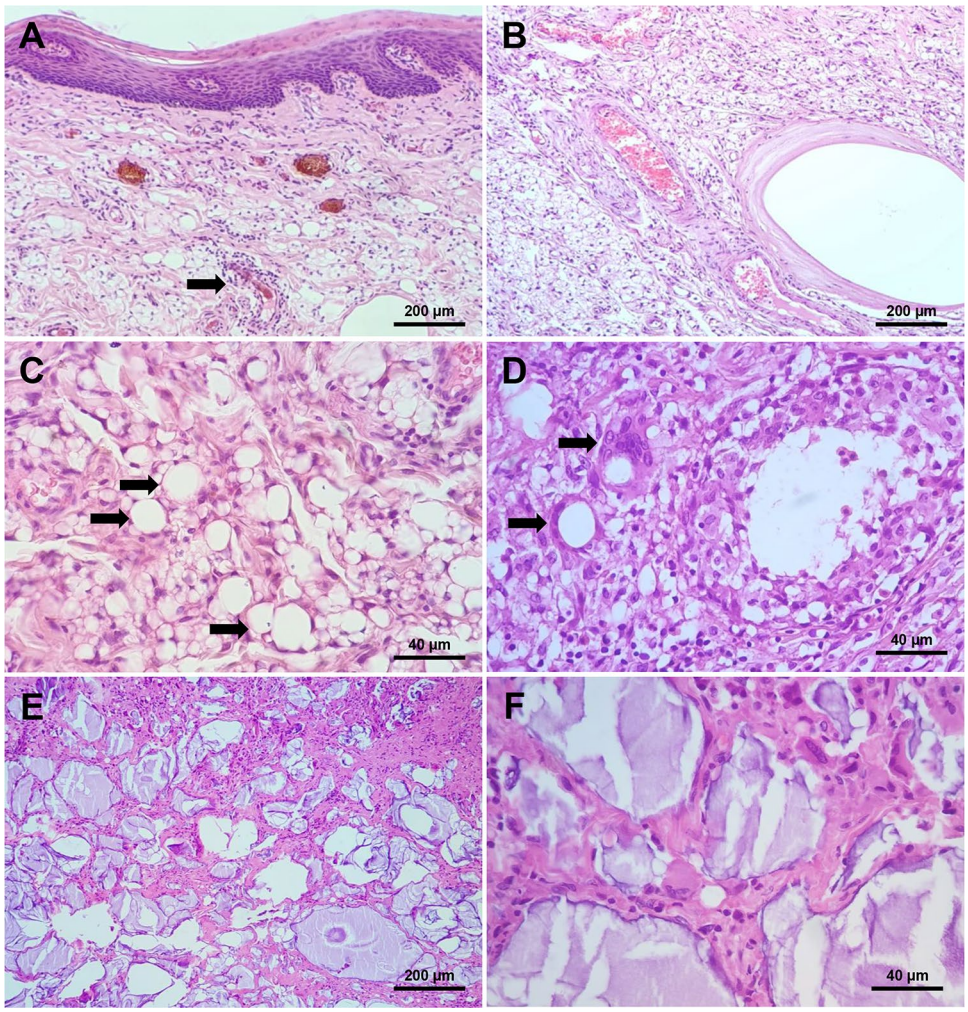

Fig. 2 Histopathological features of foreign body reactions in the oral and maxillofacial region. **A–B** Lobes formed by uniform vacuoles compatible with polymethylmethacrylate. The lobes are separated by septa of connective tissue and vasculitis (black arrow). **C–D** In detail, vacuoles (black arrows) compatible with polymethylmethacrylate show a homogenous shape and different sizes and are surrounded by numerous foamy histiocytes/macrophages. **E–F** Amorphous basophilic material compatible with hyaluronic acid surrounded by numerous foamy histiocytes/macrophages and multinucleated giant cells (black arrows) (hematoxylin and eosin stain; original magnifications: ×4 and ×20)

surrounded by macrophages, multinucleated giant cells, and mononuclear inflammatory cells [3, 6, 7, 19]. Conversely, cases of polymethylmethacrylate-associated foreign body reactions have been morphologically defined as numerous well-defined round-to-oval vacuoles, some of them surrounded by multinucleated giant cells. Multinucleated giant cells may exhibit asteroid bodies along with vasculitis [3, 7, 17–21]. The presence of asteroid bodies was not observed in our cases; nonetheless, we identified polymethylmethacrylate by the presence of homogenous vacuoles of similar shape and size that corresponded to its microspheres, which can be at least 20 µm in diameter [17]. Unlike polymethylmethacrylate, adverse reactions to silicone oil and gel forms are usually accompanied by a sparser inflammatory response and the particles appear as clusters of round empty vacuoles of different sizes between bundles of collagen or within macrophages [18]. No further treatment is required once a biopsy-supported diagnosis of foreign body reactions related to dermal fillers has been rendered [1, 7].

Previous studies have highlighted that non-surgical cosmetic procedures are becoming more popular, but patients are still unaware of the relationship between the use of dermal fillers and adverse reactions, especially foreign body reactions [3, 7]. It is believed that this is one of the reasons that lead patients to omit or not inform about the esthetic procedures to which they were submitted [3, 7]. However, it is reasonable to suggest that patients usually do not bother to inform themselves about the different types of cosmetic fillers and their benefits and disadvantages, or to stay informed about the filler materials and the technique employed in the procedures [22].

The shortcomings of this study concern its retrospective nature and also the fact that most clinicians had difficulty in with follow-up. Despite this, this study adds to the data on the adverse reactions to injected filler, particularly hyaluronic acid, with a prior reported incidence of late inflammatory reactions of 1.1% per year [23]; the occurrence of complications involving the oral and maxillofacial region in this study was 17.1%.

In summary, cosmetic dermal filler procedures in the oral and maxillofacial region may cause foreign body histiocytic reactions. Women in their sixth decade of life are

most affected. The lesions presented with swelling or were nodular, manly involving the lips. Histopathological data of foreign body reactions can help identify the dermal filler used, especially when patients do not provide information about the procedures performed.

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Author Contributions GR, BABA and MVD conceived the presented idea. JLL, NG, RPA, and MGG were responsible for the clinical management of cases. GR, ILC, CCSB, and JAAA. wrote the main manuscript text and CHF prepared Figs. 1 and 2. All authors reviewed the manuscript.

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Data Availability Not applicable.

Code Availability Not applicable.

Declarations

Conflict of interest The authors have no conflicts of interest to declare.

Ethical Approval Data were collected in accordance with guidelines from the institutional Research Ethics Board (No. CB-062-2018).

Consent to Participate No identifier information is included in the study, which meets the waiver criteria for the institutional review board of Universidad Central de Venezuela.

Consent for publication Written informed consent was obtained from the participants for data collection and publication of this study and accompanying images.

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