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Chronic lip edema and pain secondary to lip augmentation procedure: histological, scanning electron microscopy and X-ray microanalysis evaluation

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Abstract. – BACKGROUND: In parallel with the increase in requests for filler injections, reported complications (immediate or delayed and transient or permanent) increased too.

CASE REPORT: In the presented case report, a patient reported a delayed complication of filler injection. The complaints of the patient and the objective evaluation revealed the presence of multiple lip nodules, that were painful both spontaneously and at the touch, after 10 years from a lip filler injection. The surgical excision of the neoformations permitted the complete healing of the lesions. The histological analysis showed a not specific pattern, showing a material encapsulated by a tissue reaction, confirming that the possible cause of the multiple injuries could be attributable to the injection received years earlier.

CONCLUSIONS: The professional who intends to perform filler injections needs a complete training process, both from a theoretical and practical point of view. Also, the patients must be informed of the possible risks associated with each product.

Key Words:
Injectable fillers, Dermal fillers, Complications, Nodules, Hyaluronic acid, Aesthetic procedures.

Introduction

Today the cosmetic dermal filler market covers about 4.3 million procedures worldwide, and it will show a further 15.7% increase in the following years[1]. Lip augmentation procedures have become gradually more popular and common due to cultural tendencies and association of lips appearance with both beauty and youth. However, in parallel with the increase in requests, reported complications increased too. Therefore, in the last century, a large variety of injectable materials have been used for body rejuvenation. Injectable paraffin, liquid silicone, silosannic oil, calcium hydroxyapatite, and other compounds have been developed, tested, and applied with the expectation to reduce the possible complications[2]. There are many fillers on the market, each with different characteristics, indications, and implantation techniques. Based on their origin, they can be classified as natural, synthetic, and mixed. The ideal material should be safe, biocompatible, painless, stable at room temperature, not allergenic, no teratogenic or carcinogenic, easy to remove in case of complications, and inexpensive[2]. Researchers are still working to find an ideal filler that meets all these criteria. The results obtained with hyaluronic acid fillers (HA) are very good and almost always have a good level of satisfaction in the patients treated. Moreover, HA can be easily removed by hyaluronidase in the case of misinjection[3]. However, despite being almost immediate, the effects of HA are not permanent, and, after a relatively short time, few months later, the aesthetic result disappears. This happens because the body metabolizes the injected HA. In any case, it should be pointed out that the effects and results obtained with hyaluronic acid

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filler injections, although almost always good, can be different from individual to individual. They depend on skin type, concentration of hyaluronic acid, type of filler injected, treated area, health care training, and health ethics. Furthermore, the duration of the effect promoted by the injections of hyaluronic acid fillers is heavily influenced by stress, smoking, exposure to natural/artificial UV rays.

Case Report

The present case report followed the CARE (CAse REport) Statement and Checklist guidelines[4]. Moreover, the University of Chieti-Pescara, Italy, classified the present case reporting to be exempt from ethical review as it carries only negligible risk and involves the use of existing data that contains only non-identifiable data about human beings.

A female patient, V.A., 53 years old, non-smoker, with silent systemic anamnesis, absence of allergies to drugs and food substances, came to our attention. The informed consent was signed by the patient, for the documentation of the case and for the treatment. The patient complained of spontaneous pain and edema for a few months, in some parts of the lips, a sensation of something moving within them, and an increase in painful sensation to touch in the points that were already painful spontaneously. At the anamnestic interview on October 28, 2020, the patient told of a lip injection with hyaluronic acid about ten years before.

She had no documentation in her possession, nor did she remember the doctor who practiced her the filler. Since then, she did not receive any more infiltrations of fillers or any other kind of treatment in the lips. Few years after the injection she reported the appearance of multiple nodules on the lips, which were not painful at the time of their appearance. However, over time, the lesions become painful first to the touch and then also spontaneously.

Results

Objective Evaluation

At the objective evaluation, 8 knotty areas were appreciated, definitely painful to the touch and not mobile on palpation (Figure 1). An ultrasound scan was not performed as per protocol, because, at the time of the patient's evaluation, a suitable ultrasound was not available.

Management

On September 26, 2020, as per the current protocols, a hyaluronidase injection was performed in the nodule, accompanied by a systemic antibiotic and steroids administration with no clinical improvement. After two months, one neoformation present in the lips was excised for histological evaluation and reported a chronic inflammatory component in which accumulation of amorphous matrix referable to foreign material was observed. After explaining to the patient the different therapeutic options on January 28, 2021,

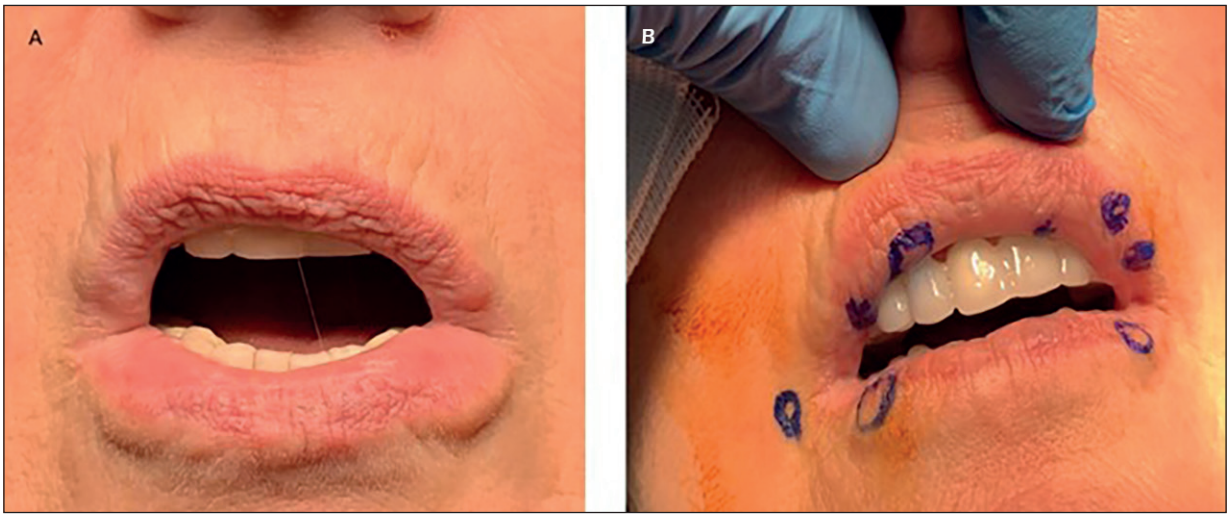

Figure 1. A, Clinical aspect of lips. **B**, Evident presence of a nodule.

the neoformations present in the lips were excised under local anesthesia achieved with 1 mL of 2% articaine/adrenalin solution (Pierrel Pharma, Capua, Italy).

The excision of the neoformations was performed by incision with a 15-scalpel blade, a full-thickness flap with the use of micro-detachers, a Hudson forceps, and a clemerin with a curved tip. A straight sharp-pointed scissors permitted the complete removal of the neoformations. The control of hemostasis was obtained with a resorbable suture 5/0 thread (Sweden Martina, Padova, Italy).

After the surgical excision, the presence of very hard irregular-shaped neoformations, similar to pebbles, was revealed, the largest of which had a diameter of 4 mm. After 1 month no scarring was observed (Figure 2).

Post-Operative Drug Therapy

The patient at home was recommended antibiotic therapy, azithromycin 250 1 cp per day for 3 days, and cold food for 1 week.

Biopsy and Histological Analysis

One of the small neoformations was sent to Prof. G. Reggiani Bonetti, of the anatomy and pathology department of the University of Modena for a histological examination. The biopsy was stored immediately in 10% buffered formalin and processed for histological analysis. These slides were stained with hematoxylin and eosin observed in normal transmitted light under a Nikon microscope ECLIPSE (Nikon, Tokyo, Japan).

Macroscopic examination

A brownish tissue of 0.2x01 cm in which a grayish hard portion of about 0.1x0.05 cm was recognized. The material has been included in its entirety.

Histology

Skeletal muscle fibers and chronic inflammatory component in which accumulation of amorphous matrix referable to foreign material was observed (Figure 3).

Histological conclusions

A chronic inflammatory reactive tissue, in relation to exogenous material (Figure 3) was found.

SEM and Electron Spectroscopy Evaluation

The paraffin has been removed from the specimen and observed under the microscope. The specimen was observed by SEM (SEM, JSM-6480LV; Jeol, Tokyo, Japan), to evaluate the surface topography. The chemical composition of surfaces was evaluated by electron spectroscopy (AES, PHI 700; ULVAC-PHI Inc., Kanagawa, Japan) employing a 10 kV/10 nA electron beam energy to characterize the near surface of the specimen (0.5-3.0 μ) elemental composition. The specimen was taken from their original package directly from the supplier. It was placed on an aluminum stub with sticky conductive carbon tape. The surface was examined with a field emission environmental scanning electron microscope. Pictures were taken in both secondary and backscattered electrons. Some different electron-dense and electron-lucent areas were

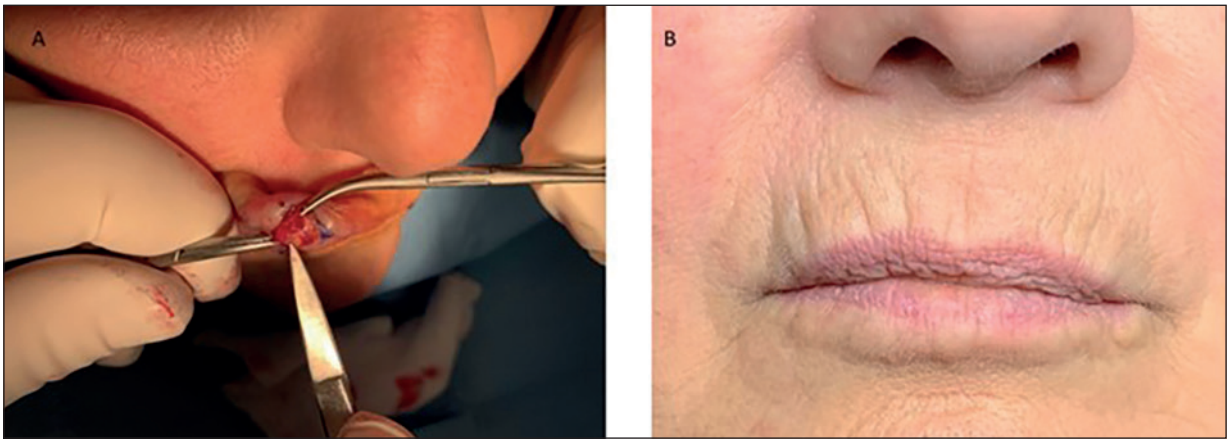

Figure 2. A, Surgical remove of the nodule. **B**, Full up after one month, no scarring was observed.

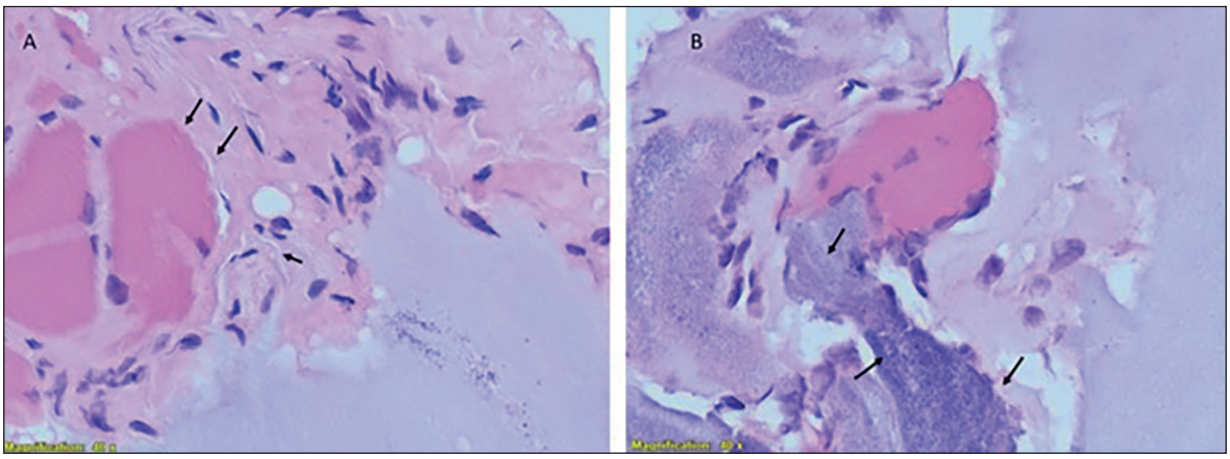

Figure 3. **A**, Histological image showed a soft tissues and amorphous substance (Arrows). Hematoxylin and Eosin staining ×30. **B**, A hight magnification was observed chronic inflammatory cells infiltrate (Arrows). Presence of macrophages and amorphous substance. Hematoxylin and Eosin staining ×30.

detected, in these areas the X-ray spectroscopy (XPS) analysis indicated an increased Ca and P concentrations on the surface. The ions distribution on the surface was Carbon (C) 21.61%, Oxygen (O) 25.43%, Fluorine (F) 4.20, Sodium (Na) 1.03%, Silicon (Si) 0.0%, Phosphorus Chlorine (P) 16.11% and Calcium (Ca) 31.62%, while in the electron-lucent areas the ions distribution on the surface was Carbon (C) 77.76%, Oxygen (O) 17.43%, Fluorine (F) 2.24, Sodium (Na) 1.37%, Silicon (Si) 0.64%, Phosphorus Chlorine (P) 0.74% and Calcium (Ca) 00.00% (Figure 4).

Follow-Up

The patient came back to our attention for control at 7 and 15 days, demonstrating excellent compliance (Figure 3). Three months after surgery, the patient is still re-evaluated through clinical inspection; there are no more swollen areas with painful nodules spontaneously or on palpation.

Discussion

The histological outcome of the present clinical case showed a foreign body reaction, while the SEM and EDS analysis showed a high presence of calcium and phosphorus chlorine. Calcium and phosphorus chlorine are two components of mineral tissues[5,6], indeed the patient had calcified nodules. These outcomes suggest

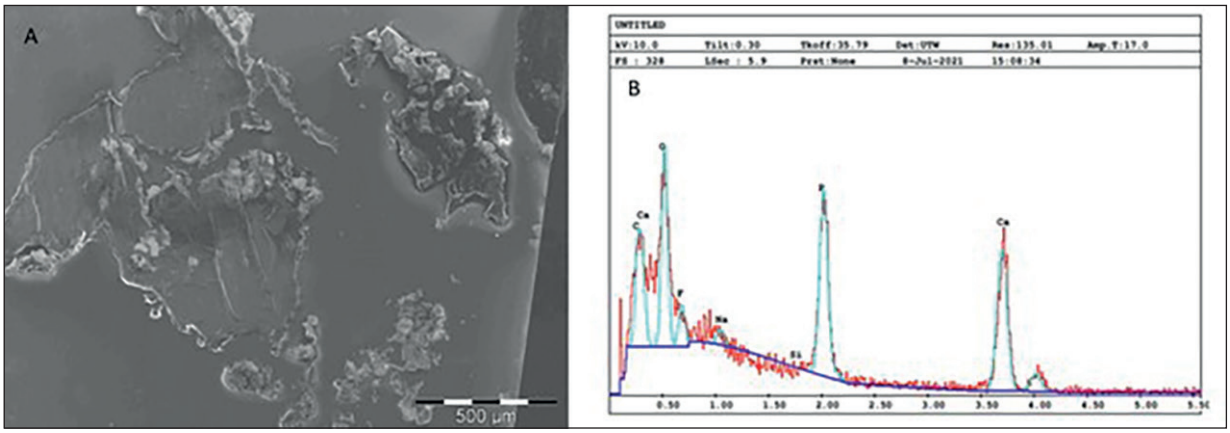

Figure 4. **A**, SEM analysis showed an electron dense area (Bar=500 µ). **B**, EDS analysis showed a hight Calcium and phosphorus chlorine.

that a higher quantity of calcium could be due to calcification in response to injected material or that the patient received a filler enriched with hydroxyapatite[7]. However, histological analysis showed chronic inflammatory cells infiltrate that entraps a foreign body. These data suggest the inability of the enzymatically degradation by immune system or through phagocytose of the foreign body[8,9]. Lips augmentation procedure has increased in the following years because the mouth is placed in the center of the face and influences the rejuvenated appearance of the face. The filler complications can be classified, accordingly with the onset of the adverse events, as early and delayed complications or accordingly in ischemic complications and nonischemic[8,10,11]. They can also be distinguished, accordingly, to the severity of symptoms in mild and severe ones[2]. Moreover, based on the duration of the events, the symptoms can be transient or permanent. With the increase of the request for filler injections also the incidence of adverse reactions is increasing. A recent retrospective study[9] analyzed the occurrence of dermal filler complications in the USA between 2007 and 2017 associated with three biodegradable injectable substances: calcium hydroxylapatite, hyaluronic acid, and poly-l-lactic acid. Based on 5,024 reported events, the most commons (>10% of the events) were represented by nodule formation, infection, inflammation, allergic complications, and vascular complications[12]. However, it should be considered that in the same years about 18 million injections have been estimated in USA[13]. In the presented case, the presence of nodules represented a severe complication for the patient, both for the pain suffered and also for the esthetical problems that were acerbated by the fact that were caused for an esthetical treatment.

The histological feature of the biopsy suggests as a primary cause for the onset of the complication, a foreign body reaction, confirming that the possible cause of the multiple injuries is attributable to the injection received years earlier. The histological pattern was in contrast with our previous study[14], in which cross-linked hyaluronic acid showed no inflammatory response, tissue contractions, and no local flogistic evidence just after 60 days from the injection. Also, in another study[15] the use of dermal filler containing fragments of hyaluronic acid between 20 and 38 monomers and amino acid, showed at 3 months no inflammatory reaction, but an increased fibroblast activity and vessel formation.

Considering that the patient had no specific data about the material injected, this complication could be a consequence of both the composition of the filler, but also the inappropriate management of the professional during the injection.

Indeed, the use of specific algorithms have been developed, in order to reduce immediate and delayed complications of filler injections, like warm compress, massages and the use of hyaluronidase for the degradation of hyaluronic acid[2,12].

Conclusions

The lack of knowledge of these easy, but important, maneuvers expose patients to the risk of adverse effects. The pathogenesis of these tissues' reaction remains unknown in many clinical situations.

So, to be ethically correct, the professional who intends to perform filler injections needs a complete training process, both from a theoretical and practical point of view. Also, patients must be informed of the possible risks associated with each product[12].

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Authors' Contribution

All authors were involved with the literature review and performance of the surgery. All authors read and approved the final manuscript.

Ethics Approval

The requirements of the Helsinki Declaration were observed, and the patient gave informed consent for all surgical procedures. This study was conducted in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki and the additional requirements of Italian law.

Informed Consent

Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

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