Imaging in dermal fillers

Francesca Romana Grippaudo

cmb.

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Stellingen

1. "Personal beauty is a greater recommendation than any letter of reference". *Aristotle. (Philosopher ;BC 384-BC 322).*

2. "Everything has beauty, but not everyone sees it". *Confucius (Philosopher and reformer;BC 551-BC 479).*

3. Improve beauty may present unexpected costs, not only financial, but in terms of health.

4. Be aware of the unknown. Always search for knowledge and act with wisdom

5. High Frequency Ultrasound has proved to be a useful tool in identifying liquid silicone or other dermal fillers implanted in subjects for cosmetic purposes *(this Thesis, Chapter 3).*

6. To be able to detect with High Frequency Ultrasound the presence and nature of a filler in absence of medical documentation, before attempting further treatments can reduce complications (*this Thesis*, *Chapter 4).*

7. In complicated patients Magnetic Resonance Imaging with contrast media is useful to anatomically define the extent and infiltration of the filler, useful information for the plastic surgeon (*this Thesis*, *Chapter 5).*

8. Radiolabelled White Blood Cells scintigraphy is the most accurate imaging method for differential diagnosis between an inflammed and infected filler (*this Thesis*, *Chapter 6).*

9. "There are more things in heaven and earth, Horatio, than are dreamt of in your philosophy". *Hamlet act 1, scene 5, 159-167, Shakespeare (Poet 1564-1616.)*

10. "Magister alius casus" *(Misfortune is a second master; Pliny the elder 23-79).*

11. "The world is a book, and those who do not travel read only a page". *St. Augustine (Theologian 354-387).*

ISBN: 978-90-367-6230-4

The work presented in this thesis has started at the University of Roma "La Sapienza", where most of work has been performed. Some articles have been made in collaboration with the University Medical Center Groningen, NL.

Cover picture:

All purpose fillers not for cosmetic enhancement.

RIJKSUNIVERSITEIT GRONINGEN

Imaging in Dermal fillers

Proefschrift

ter verkrijging van het doctoraat in de

Medische Wetenschappen

Aan de Rijksuniversiteit Groningen

op gezag van de

Rector Magnificus, dr. E. Sterken,

In het openbaar te verdedigen op

Maandag 13-05-2013

om 12:45 uur

door

Francesca Romana Grippaudo

geboren op 13 januar 1961

te Roma, Italië

Promotores:

Prof. dr. A. Signore

Prof. dr. N. Scuderi

Beoordelingscommissie:

Prof. dr. M. Oudkerk

Prof. dr. C. van de Wiele

Prof. dr. B. de Lei

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Chapter 1

Introduction

Cosmetic tissue augmentation and the correction of skin depressions using injectable material is no new concept. During the mid 1900's, paraffin injections were proposed by the doctors as a skin filler to correct tissue depressions, scar or rhytids (1). After the injection in the soft tissues, paraffin lead to unpleasant side effects and high incidence of granuloma, and its use was discouraged.

The next attempted substance used was the highly refined, medical grade silicone. Liquid silicone injection in the soft tissue of the human body was introduced in 1940 with the purpose to be encapsulated by the body's own connective tissue, and to remain for a prolonged time span, to fill soft tissue deficiencies permanently or for cosmetic enhancement (2, 3). This material gained popularity for a decade, for its ease of use and for the immediate satisfactory results (2). It was then discontinued in mid-70's and 80's due to the high percentage of late complications (3-5). The use of liquid silicone, as an agent for cosmetic dermal filler, has therefore been prohibited in many countries: in 1992-1993 in Italy and most European countries, and in 2010 in United States by the Federal Drug Administration who stated that "*the use of liquid silicone or silicone gel for injection has not approved to fill wrinkles or augment tissues anywhere in the body*" (6, 7). Even if this application is prohibited, it is still possible to see patients, mainly from third world countries, whose soft tissues are infiltrated with silicon oil because of its low cost. In other countries facial augmentation with medical grade liquid silicone is still an acceptable practice and its use is divulgated by the current medical literature (4, 8). Liquid silicone complications appear in the long term (after years) and consist of migration of the product in the soft tissues and

even in the lymph nodes, generation of lumps and/or granulomatous lesion, sometimes so severe to simulate a neoplasm (9, 10).

In the last decades many new materials were introduced in the market claiming to be permanent, inert, non allergenic, well tolerated, non migrating and easily removable in the rare event of complications (11,12). These injectable fillers are made from various materials and can be divided in classes according with the temporary, long lasting or permanent effect in the soft tissues (13).

Temporary fillers are completely reabsorbed after 3 to 15 months from their injection in the soft tissues and are composed by collagen and hyaluronic acid. Collagen derived by bovine requires a skin test, before its use, to exclude allergic reaction to the product. Recently, were introduced in the market highly purified cross linked collagen derived by porcine tendons not requiring a skin test. Hyaluronic acid (HA) based dermal fillers are the most diffuse dermal fillers with more than 10 years of clinical data proving its safety and efficacy (13).

Long lasting fillers stay in tissues up to 24 months prior their degradation and are composed by polylactic acid (14) and hydroxilapatite (15). Poly-lactic acid claims to stimulate fibroblast to produce more collagen. Radiesse, composed by 30% calcium hydroxilapatite and 70% carrier gel containing sodiumcarboxymethyl-cellulose, glycerine and water, once injected in the soft tissue form a temporary scaffold, reabsorbed in 2 years time, within which the patients own tissues grows new collagen cells.

Permanent fillers, introduced in the market from the mid 1990's, are designed to be encapsulated by the body's own connective tissue and remain permanently to fill soft tissue deficiencies or for cosmetic enhancement. They are composed by polymethylmethacrylate with or without collagen as a vector (Artecoll®, Metacrill®), (16), to polyacrylamide hydrogel - PAAG (Aquamid®, Royamid®, Formacryl®). (17), to polyalkylamide (BioAlcamid®) (18), to acrylic hydrogel (Dermalive®), (11), to silicone particles suspended in a polyvinylpirrolidone carrier (Bioplastique®),

(19). The application of permanent fillers require a learning curve and a proper patient selection, but gained wide popularity soon after their introduction.

Despite the minimally invasive nature of the dermal fillers, there could be some complications related to them.

Common complications in the short term (soon after the treatment) are bleeding or bruising, redness of the site of injection and oedema, claiming to resolve spontaneously in few days (20). There is always a risk of technical fault for overcorrection or because the product is injected in the wrong site. The long term complications (after six months from the treatment) are the formation of foreign body abscesses and granuloma, recurrent infections healing with the onset of fibrotic tissue, migration of the product, ulcers and fistulas (20). Because permanent dermal fillers diffusely infiltrate the soft tissues, once a complication appear, it is very difficult or impossible to remove them completely in order to achieve a healing process (21). To further complicate the diagnostic pathways patient often ignore the nature of the dermal filler implanted.

Imaging in dermal fillers

Scattered reports appeared in the literature to show the imaging of dermal filler, mainly to show the complications (22).

High Frequency Ultrasound (US) was used to study healthy and pathologic soft tissues (23-25). It was therefore logical to explore the potentials of this technique as a diagnostic tool in normal and pathological fillers implants in the soft tissues.

Similarly, Magnetic Resonance Image (MRI) represents a good technique to visualise the soft tissues, especially with the aid of contrast media (26), so it was hypothesized a role of this technique in the visualization and diagnosis of the dermal filler complications.

Nowadays, the gold standard for imaging infection is represented by the scintigraphy with radiolabeled autologous leukocytes that is very

sensitive and specific for many infection processes (27,28). It can be logical to suppose a role for nuclear medicine imaging in dermal fillers complications for diagnosis of subclinical infections.

In summary, diagnostic imaging can be very important for managing patients with suspected dermal filler related complications and different technologies may have complementary roles.

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Chapter 2

Ultrasound assisted liposuction for the removal of siliconomas

Francesca R. Grippaudo[1]; Cristina Spalvieri[1]; Alfredo Rossi[2]; M. Giuseppina Onesti[1]; Nicolò Scuderi[1]

[1]Plastic Surgery Department, University "La Sapienza", Rome, Italy

[2]Dermatology Department, University "La Sapienza", Rome, Italy

Scand J Plast Reconstr Surg Hand Surg 2004;38:21-26

Key words: siliconomas, complications, imaging, ultrasound liposuction

Abstract

In the past, the traditional methods of removing siliconomas have been excision of the affected tissues or suction of the injected silicone. Unfortunately siliconomas are often found in exposed areas, where it is undesirable to leave visible scars, and suction is technically difficult and often unsuccessful because the affected tissues are so hard. Because we have used ultrasound-assisted liposuction for other procedures since 1984, it seemed logical to find out whether this technique would be useful to remove siliconomas. We have used it in three such patients, ranging in age from 36 to 84 years. Our mean follow up is 38 months (range 18 months-4 years). We have found that it results in improvement in all patients. The only problem was a minor burn at the entrance port in one patient.

Introduction

Silicone injection to fill soft tissue defects was popular in the past, but some of its complications have developed only years later (4,7,8,11,15,16). These are related to the injection of silicone that was not of medical grade, and the use of an excessive quantity (12), together with infiltration in an unsuitable area (such a the mammary region)(9), and late allergic reactions to the product.

Patients usually report a clinical history beginning with chronic inflammation in the area injected with silicone months or years before, followed by a progressive reddening and thickening of the tissues, and pain (12). Severe cases progress to atrophy and ulceration of the soft tissue involved, and the development of lumps (11).

It is often difficult to remove all the injected material from the affected tissue because it has migrated through the soft tissues after injection.

Radical excision of all involved tissues has been proposed, followed by reconstruction of the defect by local or free flaps (1,9,10).

Suction of the tissues affected by siliconoma have been attempted (1,2,17) with differing rates of success (18,19).

During the last five years 20 patients have presented to our centre with adverse effects of injections of liquid silicone into different parts of their bodies. All patients were studied with ultrasound and magnetic resonance imaging to localise the injected material accurately [Spalvieri C, et al. Possibilità diagnostiche nelle complicanze legate all'uso di silicone liquido. (Diagnostic tools in evaluating the complicances due to liquid silicone injections) Paper presented at the 48th National Meeting of the Italian Society of Plastic, Reconstructive and Aesthetic Surgery, 1999]. The proposed treatment differed depending on the extension and site of the foreign material: medical (local and systemic corticosteroids), or surgical (radical excision)[Onesti MG, et al. Complicanze legate all'uso del silicone liquido: nostra esperienza. (Our experience in treating liquid silicone injections complicances) Paper presented at the 48th National Meeting of the Italian Society of Plastic, Reconstructive and Aesthetic Surgery, 1999].

Three of these patients presented with widespread and symptomatic diffusion of the injected silicone in exposed areas, which was resistant to medical treatment and difficult to treat in a traditional way (radical excision and flap reconstruction) without leaving a deformity that was worse than the initial problem.

To overcome these disadvantages, and because we have used ultrasound-assisted liposuction for other procedures since 1984 (6,13,14), it seemed logical to find out whether it would be useful to remove siliconomas.

Patients and Methods

Three patients who presented with diffuse siliconomas were treated with ultrasound-assisted liposuction of the affected tissue. The ages of the patients ranged from 36 to 84. The time that had elapsed between the treatment and the onset of symptoms was between 2-10 years. The face was affected in two patients, showing diffuse migration of silicone into the soft tissues of the glabella, lids, cheeks, and lips; and in one patient both breasts and the epigastrium were diffusely infiltrated. The treated areas had became progressively hard, red and painful. The silicone was always displaced below the original location. In one patient the inflammatory process had proceeded to soft tissue atrophy and ulceration.

To evaluate the efficacy of treatment, each affected area was studied in all patients with an ultrasound scan before and after the liposuction with 7.5 Mhz, 10 Mhz, or 13 Mhz probes. An MRI (with magnets of 1.5 T, Siemens Vision Plus and Philips Gyroscan NT) was taken to evaluate the extension of infiltration and the gross amount of material to be removed. A reel for the skull was used to study the face and another reel was used for the breast area. An MRI was repeated at six month intervals for follow-up. A photographic record of all patients was obtained preoperatively and at follow-up.

All patients were admitted to hospital and operated on under general anaesthesia. The areas to be sonicated were infiltrated with ropivacaine 1.5 mg/ml plus adrenaline 1/200000 in normal saline, until they swelled. In three sessions we used the Contour Genesys system by Mentor, and in three the Sculpture by SMEI. The probe was always inserted with a shield (Mentor) or with the aid of a skin protector (SMEI). The energy delivered varied depending on the area to be treated (generally lower power was used for the face) and the duration of application was related to the effect obtained, evaluated by the surgeon. After sonication the area was evacuated with low power aspiration devices connected to a 3.5 mm Mercedes cannula.

The aspirate was collected, and part of it was sent for a scanning electron microscopy for preparation.

The material was fixed in glutaraldehyde 2.5%, dehydrated with critical point Balzers Union, metallised with Balzers Union metalliser SCD40, and studied under a scanning electron microscope (Philips 501S).

The processed aspirate was examined by electron probe microanalysis with a PV-EDAX 9008 (Philips) to detect the presence of silicone.

After each procedure iced packs were applied and antibiotics were given. Patients were usually discharged after two days with a simple dressing, and multiple sessions of manual lymphatic massage were prescribed during the first two months after operation.

The procedure was repeated more than once in two patients to achieve a better cosmetic result, as some liquid silicone was still present on follow-up MRI.

CASE REPORTS

Case 1

A patient aged 35 has had a male to female sex change in 1985 and had multiple silicone injections to the face (zygomatic archs, nasolabial folds, chin, lips, and eyelids) in 1994 to obtain a feminine contour. After three years she subsequently developed severe inflammation in all the injected sites.

On admission in 1997 she had diffuse facial swelling with ulceration on both zygomas. The tissues of both cheeks were hardened and the skin discoloured. Both lids and lips were thickened and difficult to move (Fig. 1a). Ultrasound scan and MRI confirmed the presence of diffuse siliconomas. After treatment with corticosteroids had failed we decided to try and remove the silicone from both cheeks through an incision in the pre-auricolar area with ultrasound-assisted liposuction. We excised the silicone from the lips

during the same sitting. Her symptoms were relieved the ulcers healed and her facial aesthetics improved.

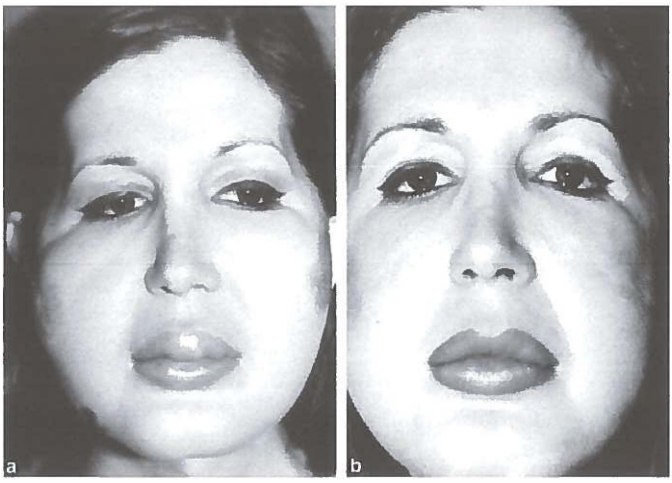

Fig. 1. (*a*) Preoperative frontal view of a 35-year-old transsexual three years after liquid silicone injections in the zygomatic area, nasolabial folds, chin, lips, and eyelids. The skin is discoloured on both cheeks, with ulcerations. The oedema of the face is severe. (*b*) Postoperative appearance after three years, having had three ultrasound-assisted liposuction sessions in the face, an upper and lower blepharoplasty, and a lip reduction procedure. Reproduced with the permission of the patient.

At six months follow-up, a MRI showed that some silicone was left in the face, so the procedure was successfully repeated in both cheeks and extended to the chin area through a submental incision. After a further 10 months the treatment was repeated for the third time in the zygomatic area, nasal folds, and chin. More silicone was also removed from the upper and lower lids. The result at 18 months follow up was good with remission of her symptoms (Fig. 1b).

Case 2

A woman aged 84, had had multiple medical grade silicone injections in 1985 to treat wrinkles in the forehead and nasolabial folds. Five years after the treatment her skin became discoloured over all the treated areas, progressing to fixation of skin to the underlying soft tissues, and formation of nodules. She subsequently developed multiple episodes of severe inflammation of the face, leading to many admissions to hospital during the following eight years. Treatment with corticosteroids was

unsuccessful, and on admission in 1998 she presented with no movement of the face, and a severe impairment in all functions of the lips. Her face was swollen and red, and the soft tissue was firm (Fig. 2a). An ultrasound scan and MRI confirmed the presence of diffuse siliconomas. Ultrasound-assisted liposuction through mediofrontal and preauricolar incision was followed by immediate improvement of the aesthetics and functioning of the face. At 6 months follow up a MRI showed some silicone left in the cheek area. One year after the first ultrasound-assisted liposuction, the treatment was repeated with further amelioration of both the functional and the cosmetic aspect (Fig. 2b). At 3 years follow up the patient was still free from disease.

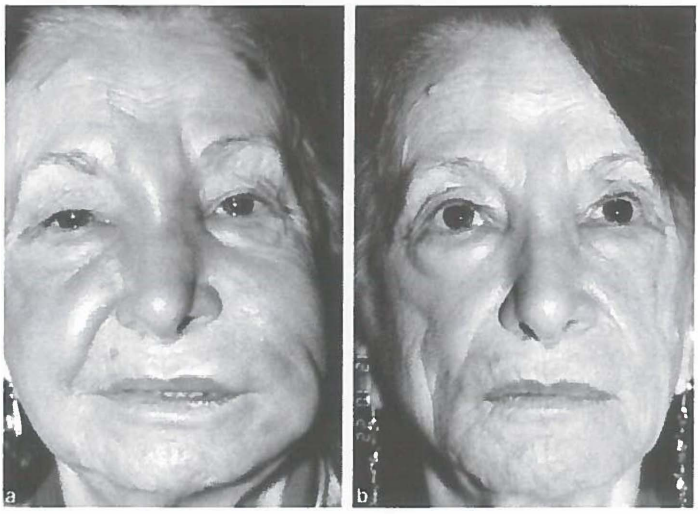

Fig. 2. (*a*) Preoperative frontal view of an 85-year-old woman 13 years after injections of medical grade silicone in the glabella and nasolabial folds. Note the "bossing" in the glabella, and the tumescence at the right nasolabial fold. The patient cannot close her lips completely because of severe inflammation of the tissues. (*b*) Postoperative appearance after 30 months, and two ultrasound-assisted liposuction sessions in the face. Reproduced with the permission of the patient.

Case 3

A woman aged 40, has had multiple silicone injections to enlarge both breasts in 1988 in South America. After 10 years she developed skin discolouration, cellulitis, and hardening of tissue in the thorax, which slowly extended to the soft tissue of the upper abdomen. On admission in 1998 both breasts were hard, lumpy, and tender, and the upper abdomen was firm and painful (Fig. 3a). Ultrasound and MRI scans showed massive diffuse infiltration of silicone in both breasts and the upper abdominal region (Fig.

3b). Bilateral subcutaneous mastectomy with skin resection and immediate reconstruction with implants was done to remove all the foreign material from the breasts. To remove the silicone that had migrated to the abdomen we used ultrasound-assisted liposuction. At 4 years follow up the patient was free from disease (Fig. 3c).

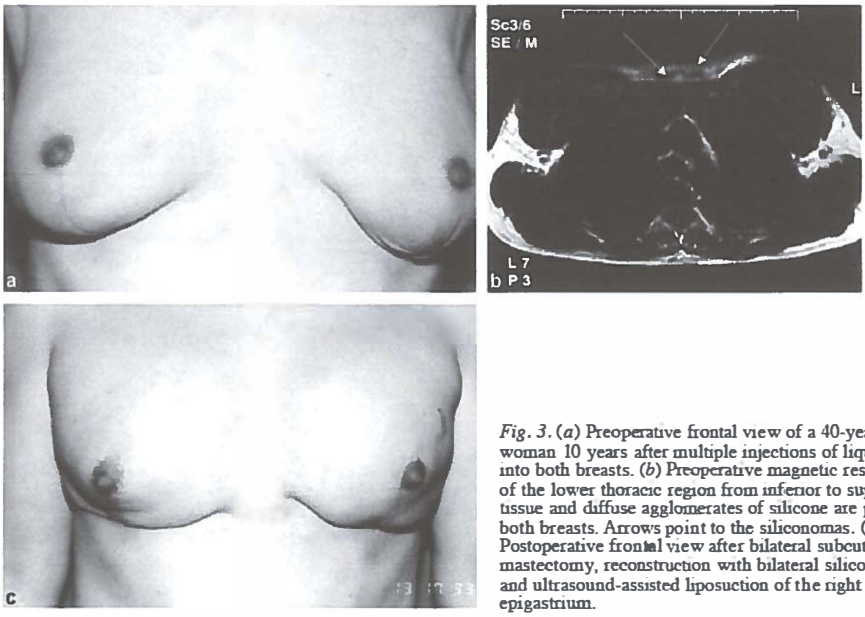

Fig. 3. (*a*) Preoperative frontal view of a 40-year-old woman 10 years after multiple injections of liquid silicone into both breasts. (*b*) Preoperative magnetic resonance scan of the lower thoracic region from inferior to superior. Scar tissue and diffuse agglomerates of silicone are present in both breasts. Arrows point to the siliconomas. (*c*) Postoperative frontal view after bilateral subcutaneous mastectomy, reconstruction with bilateral silicone implants, and ultrasound-assisted liposuction of the right and left epigastrium.

Results

All patients had immediate relief of pain and softening of the tissues after the ultrasound-assisted liposuction. It was possible to repeat the treatment more than once in the same area if indicated by the presence of silicone left after the first operation and to further improve the aesthetic result, without the onset of complications.

The only complication was one minor burn at the entrance port of the probe, which healed without consequences, and was the fault of the operator. We found no prolonged swelling as referred to by others using traditional liposuction (20).

Comparison of preoperative and postoperative MRI in all patients showed a reduction in the amount of silicone evident after each treatment (Fig. 3c, 4a, b, 5a, b).

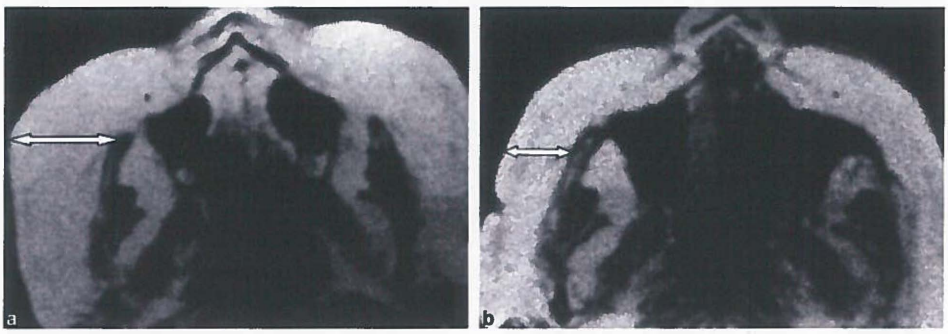

Fig. 4. Case 1. (*a*) Preoperative magnetic resonance scan of the middle third of the face. The soft tissue of both cheeks are diffusely infiltrated with silicone. Arrows show the infiltrated soft tissue. (*b*) Comparative postoperative scan of the same region after one treatment with ultrasound-assisted liposuction to the cheeks. Arrows show that the thickness of the soft tissues has diminished.

The analysis of the processed material collected after the evacuation of the sonicated tissue on scanning electron microscopy, showed fragments of acellular tissue with silicone (Fig. 5c) and drops of silicone (Fig. 5d). The specimen examined by electron probe microanalysis showed high contents of silicon (Fig. 5e).

Discussion

Serious complications after silicone injections are usually treated medically or by an en-bloc excision of the affected tissues. However in exposed areas such as the face this treatment is not always feasible, particularly if the disease is diffuse. Prolonged treatment with corticosteroids may be of transient benefit but it will not effect a cure (11). Ultrasound-assisted liposuction has given satisfactory aesthetic and functional results in all patients, with a reduction in tissue's thickness and the return of normal skin texture. Clinical symptoms were greatly reduced or eliminated

after the first treatment. The treatment can safely be repeated, even if it is impossible to remove the silicone completely with liposuction.

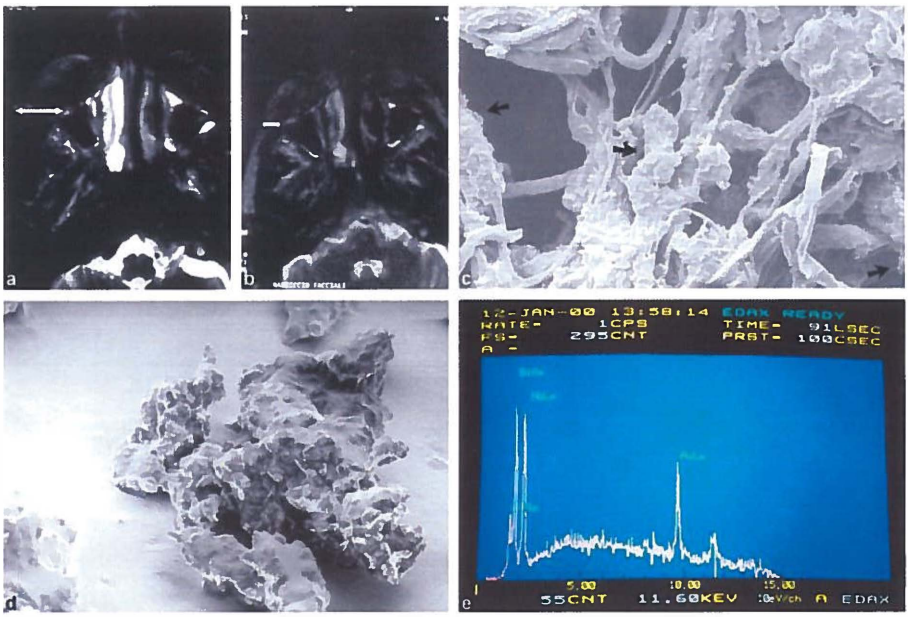

Fig. 5. Case 2. (*a*) Preoperative magnetic resonance scan of the middle third of the face. The soft tissues of both cheeks are diffusely infiltrated with silicone. Arrows show the areas of infiltrated soft tissue. (*b*) Comparative postoperative scan of the same region after one treatment with ultrasound-assisted liposuction to the cheeks. Arrows show that the thickness of the soft tissues has diminished. (*c*) Scanning electron micrograph (magnification × 2250) showing silicone (arrows) surrounded by collagen fibres. (*d*) Scanning electron micrograph (magnification × 5500) showing piece of silicone after processing of the sonicated material that was collected at the end of the ultrasound-assisted liposuction procedure. (*e*) Representative spectra of silicone identified in the fragment of specimen showing high contents of silicone (Si$K\alpha$) indicated by the first peak from the left. The aluminium (Al$K\alpha$), molybdenum (Mb$L\alpha$), and gold (Au$L\alpha$) peaks are the result of the stab and metallisation of the sample.

Zandi claims to have abandoned the procedure of suctioning the liquid silicone from the soft tissue because of lack of success (18,19) and questioned the success that other authors have obtained (1,3) in removing the silicone. From our experience we agree with Zandi that complete suction of the liquid silicone from the soft tissue is difficult, but a reduction in the amount of the silicone it is always within reach with ultrasound-assisted liposuction. All the patients described achieved long lasting remission after all other treatments had failed and in the absence of any feasible surgical options.

In our experience it is possible to effectively remove the silicone from the tissues, illustrated by the decrease in the amount of silicone diffused in the tissue in the postoperative MRI.

Scanning electron microscopy confirmed the removal of silicone found in the aspirate, and the electron probe microanalysis is a highly sensitive and specific way to identify silicone within a tissue sample ($_5$). The oligo element analysis of the sonicated material made in this study, detected a strong peak of silicon, which is normally absent from healthy tissues, and proved the aspirated material to be silicone.

In conclusion, excision of silicone remains the best choice of treatment, but it is impossible to achieve in exposed areas that have been diffusely infiltrated. To remove silicone under such circumstances, ultrasound assisted liposuction seems to be a new tool for the surgeon.

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Chapter 3

High frequency sonographic findings of temporary and permanent dermal fillers

Francesca R. Grippaudo MD, Mauro Mattei MD*

Plastic Surgery Unit, 2nd Medical Faculty, Sapienza University of Rome, Italy

*Radiology Dept., S Andrew's Hospital, Rome, Italy.

Skin Research and Technology 2010;16:265-269

Key words: dermal filler, High frequency sonography, collagen, hyaluronic acid, polyacrylamide hydrogel , polyalkylimide hydrogel , silicone

Abstract

Dermal fillers are largely used, some have a permanent effect whereas others are temporary. Aim of this study is to describe the ultrasonographic features of permanent and temporary fillers injected in patients for cosmetic purposes.

Between December 2006 and October 2009 39 subjects, aged 25 to 45, having received lips or nasolabial fold filler augmentation were enrolled for high frequency sonographic examination by a blinded investigator. Criteria of exclusion were an history of autoimmunity, infection, neoplastic diseases or episodes of local reactions to the injected filler. Twenty patients underwent sonographic exam after the injection of a temporary filler (collagen or hyaluronic acid) by the senior Author; the remaining were enrolled among patients seeking for a consultation for further cosmetic reasons, but having been treated with an identifiable filler (Aquamid™, BioAlcamid™, Matridex®, liquid silicone) before. It was always possible to identify the filler at the site of injection. The sonographic images of the investigated filler differed. Seldom it was possible to discover a silent inflammatory reaction, otherwise unsuspected. Ultrasonography has proved to be an useful, non invasive tool for the identification of the presence and the temporary or permanent nature of the filler injected.

Introduction

Cosmetic tissue augmentation and the correction of skin depressions using injectable materials is not a new concept. The popularity of this non surgical procedure is constantly growing worldwide, and many implantable substances have been introduced in the market for this purpose. Dermal fillers differ in composition and can be classified in two classes

according with their permanence in the tissue: temporary, lasting only few months prior degradation, and permanent remaining in the site of inoculation for years (1).

Collagen and hyaluronic acid have a temporary effect only and are reabsorbed over a period of 6-12 months.

Matridex ® is a biodegradable filler composed of hyaluronic acid and deextranomer particles (DEAE Sephadex) to stimulate collagenasis (2), claimed to fill the soft tissues for a longer time than collagen or hyaluronic acid.

Fillers composed by Polyacrylamide hydrogel – PAAG (Aquamid™) and Polyalkylimide- amide hydrogel (BioAlcamid™) remain permanently in the soft tissues, as well as liquid silicone (1,3). Although subcutaneous injection of liquid silicone was declared illegal in many countries, it is still in use because of the low cost compared to others fillers.

Due to the natural evolution of the aging process, patients often seek multiple tissue augmentation procedures, often at yearly distance and from different physicians.

Patients are not always aware of the materials implanted in previous treatments, and since the manufacturers of most fillers advice against the association of different materials in the same area, it can be difficult to safely perform further cosmetic procedures as required.

Up until now it was impossible, in absence of the identification label of the previous filler, to detect its composition once injected into the body, therefore increasing the risks of following treatments. Seldom it could only be presumed due to the temporary nature of some of the products, such as collagen or hyaluronic acid. Because high frequency diagnostic ultrasound has proved to be a useful tool for non invasive imaging of the healthy and pathologic skin and subcutaneous tissue (4), it seemed logical to find out whether it would be useful to investigate and describe the sonographic aspects of the diverse temporary, long lasting and permanent dermal fillers used for cosmetic tissue augmentation in healthy patients.

Materials and methods

For this study 39 healthy patients who had tissue augmentation for cosmetic purposes with a known filler underwent high frequency sonographic exam of the injected area. Site of injection were the nasolabial folds and the lips. The investigator performing the sonographic exam was blinded to the composition of the filler injected. The sample included ten patients treated 6 weeks to 3 months before by the senior Author with collagen (Evolence™, ColBar Life Science, Johnson and Johnson) and ten patients treated with hyaluronic acid (Restylane®, Q-Med ICT, Sweden). The rest of the sample included 19 patients seeking a consultation for various cosmetic procedures with an history of permanent filler treatment elsewhere over a period of 6 months to two years before, all of them showing the product proofs of identification (label or box): seven patients had Aquamid™ (Contura International, Soeborg, DK), six had Bio Alcamid™ (Polymekon, Brindisi, Italy), two Matridex® (BioPolymer GmbH & Co, KG). In the sample were included 4 patients reporting the injection of liquid silicone.

The study population did not show or report any local or general complication related to the filler.

Other patients presenting with local or general complication after filler injection were excluded from the present study, as well patients affected by autoimmune disease, neoplasy or infections.

The study group underwent a US scan by a physician blinded by the filler injected.

Patients all had their upper lip or nasolabial fold scanned using high-frequency ultrasound, according with the site of filler augmentation.

The exam was performed with a Hitachi H21 (Hitachi Medical Corporation, Tokyo, Japan), with a high-resolution probe 10-13MHz small parts.

Ultrasound gel (Aquasonic gel 100, Parker Laboratory, Fairfield, NJ) was applied on the site to explore, and often a silicon gel pad (Aquaflex, Parker Laboratory, Fairfield, NJ) was interposed between the probe and the skin.

Once the filler was detected the scan image was acquired and saved. Using the sonoCT software program it was possible to take measurements of the filler and soft tissues.

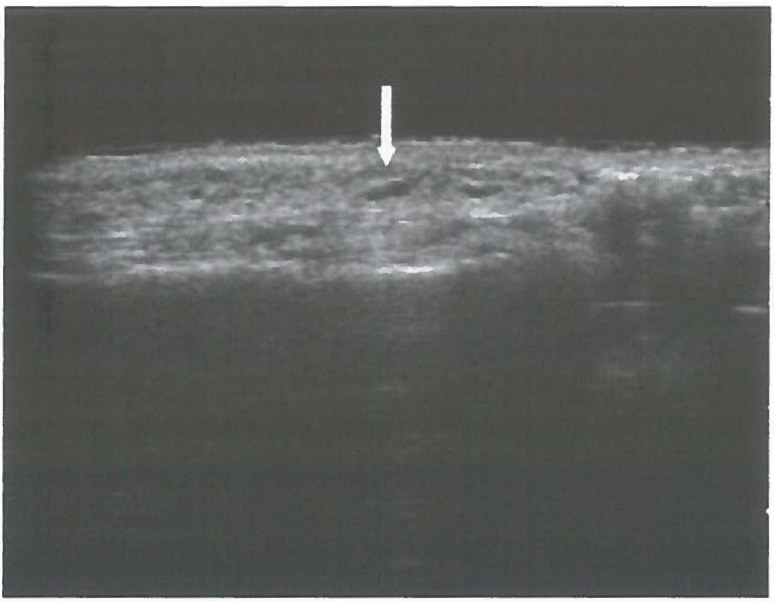

Fig. 1. Collagen (Evolence™) implant for nasolabial fold augmentation, 11 weeks after the procedure. Arrows shows many well defined regular hypoechoic masses in the subcutaneous tissue, without any signs of internal echoes. The Aquaflex pad was interposed between the probe and the skin.

Results

In all the study population it was possible to visualize the filler implanted in the subcutaneous layer. The exam was reported by the patients as quick and comfortable.

Temporary fillers (collagen and hyaluronic acid) showed as a well defined regular hypoechoic mass in the subcutaneous tissue, without any signs of internal echoes (fig 1 e 2). No differences in images characteristic of reflectivity and echogenicity consented the identification between collagen of hyaluronic acid.

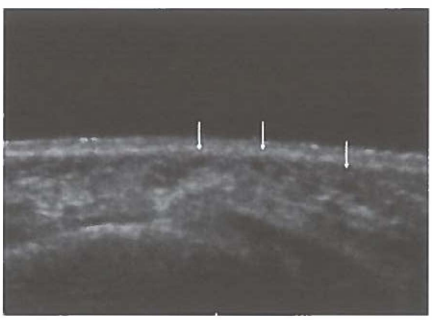

Fig.2. Hyaluronic acid (Restylane®) implant for nasolabial fold augmentation, 10 weeks after the procedure. Arrow shows a well defined regular hypoechoic mass in the subcutaneous tissue, without any signs of internal echoes. The Aquaflex pad was interposed between the probe and the skin.

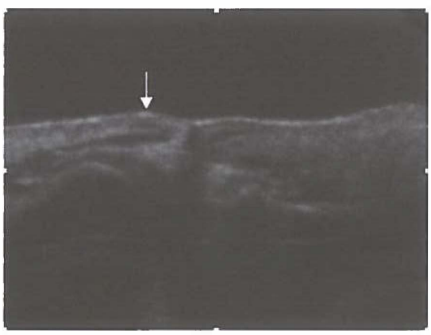

Fig.4. Aquamid™ implant for upper lip augmentation 2 years after the procedure. Arrow shows a hyperechoic mass with linear diffusion of the material. The Aquaflex pad was interposed between the probe and the skin.

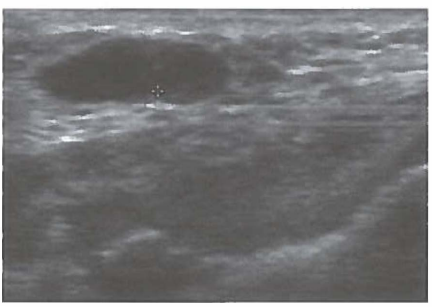

Fig.3. Matridex® implant for nasolabial fold augmentation 14 months after procedure. Sonographic pattern is of an hypoechoic image. The cross point areas of middle density within the image.

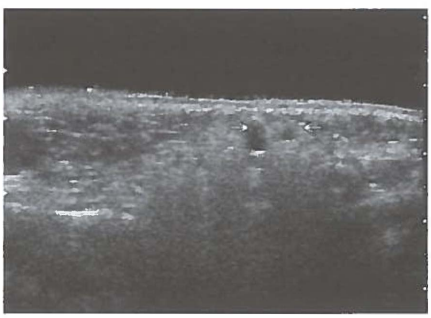

Fig.5. Bio Aquamid™ implant for naso labial fold augmentation 2 years after the procedure. Arrows show two hyperechoic images in subcutaneous tissue. An hyperechogenic halo is surrounding the implants. The Aquaflex pad was interposed between the probe and theskin.

Sonographic pattern of Matridex® is a hypoechoic image with some areas of middle density within the mass due to low level echoes (fig 3). Sonographic pattern of permanent fillers as Aquamid™(fig 4) and Bio Alcamid™ is similar and shows an hyperechoic mass, with a denser image if compared to Matridex®, and containing spot of linear diffusion of the material with small nodules. In some of the sonographic images of Bio Alcamid™, an irregular pattern of hyperechoic material within the filler implant was observed, surrounded by hyperechoic halo, as for fibrotic reaction (fig 5).

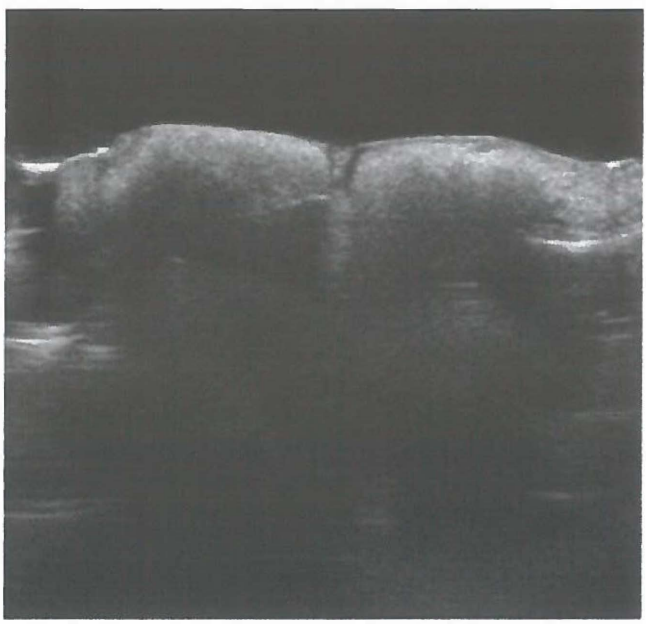

Fig.6. Liquid silicone for upper lip augmentation 2 years after the injection. It is possible to visualize a strong echogenic noise, just below the vermilion, obscuring the surrounding soft tissue, with the typical 'snowstorm pattern'. The Aquaflex pad was interposed between the probe and the skin.

Sonographic pattern of liquid silicone is of strong acoustic shadowing obscuring the surrounding soft tissue, with the typical "snowstorm pattern" presenting a well defined anterior margin and a posterior loss of details (fig 6).

Discussion

Scattered reports have appeared in the literature showing the sonographic aspect of various dermal fillers, mainly to ascertain the cause of local complication (5).

In this study healthy patients only were enrolled, with the aim to investigate on the non pathologic image of the abovementioned temporary and permanent fillers. Our findings show that all sample having received temporary fillers as Collagen or Hyaluronic Acid have a typical hypoechoic pattern, whereas permanent fillers composed by acrylic hydrogel as Aquamid and Bio Alcamid have an hyperechoic pattern. Matridex has a sonographic pattern in between temporary and permanent filler because is hypoechoic but with denser areas within the image.

Young et al. (6) have showed that high-frequency diagnostic ultrasound represents a useful tool to detect and measure temporary filler implanted in the lip. The technique used to carry out the exam in our study differs from the one adopted by Young, because a gel spacer, the Aquaflex pad, was interposed between the probe and the skin when the filler was very superficially located in the skin, to overcome the lack of resolution in the first 2 – 3 mm. This improvement consent to avoid any tissue compression, whilst providing a fixed 2 cm depth to make simpler visualize difficult near field areas and superficial structures.

In the study all sample having received temporary fillers showed a typical hypoechoic pattern and did not showed any fragmentation or relocation or reabsorption of the filler as hypothesized by Young, but this is

probably a consequence of the short time elapsed between the injection and the exam.

In this study all patients treated with temporary filler did not showed any sonographic sign of inflammation. After this study it is possible to report that nature of the tested temporary fillers can be always identified because they do not induce any reaction in the surrounding tissues.

Indrizzi and coworkers examined the use of ultrasound imaging in detecting the time changes of Bio Alcamid™ after its implant in soft tissues for reconstructive purposes (7) from 7 days to 36 months. They reported, but did not showed in figure, an image change from the anecogenous mass of recent implants only to corpuscolated mass with ageing of the material. We have never observed any anechoic image after Bio Alcamid™, but we evaluated patients with older implants only.

Although all of the patients who received Bio Alcamid™ did not showed or reported any clinical sign of local pathology, the sonographic pattern of inflammations and/or foreign body reaction were sometimes detected.

While evaluating the interactions between filler and biologic tissue it is important to remember that the border between physiologic and pathologic response leading to an adverse events often is only quantitative. A minimal fibrotic reaction it is considered part of the process to gain the desired cosmetic result. However, if the reaction is excessive, it may cause complications as the formation of scar tissue or giant cell foreign body granuloma that can be either visible and palpable.

The injection of medical grade silicone for cosmetic purposes is illegal in most countries in the world. It was first used in Asia and later introduced in Europe and South America. Sometimes industrial grade silicone is used by unlicensed personnel for cosmetic reason because of the low cost of the material.

Until mid 90's silicone was considered to be one of the most inert materials available in medicine and its use in wrinkle correction or lip

augmentation was widespread, but toxicity studies on animals and humans showed significant late reactions to silicone treatments (8, 9).

In this study it was always possible to identify liquid silicone because of its peculiar pattern, as previous studies have shown (5, 10).

Conclusion

As shown from our results, filler sonographic localization and measurement was possible in 100% of the cases.

High frequency diagnostic ultrasound has proved to be a useful tool in identify the liquid silicone or the permanent, semi permanent and temporary nature of the filler implanted in a healthy sample for cosmetic purposes.

The exam was user friendly, quick, cost effective and very well tolerated by the patient.

Introducing this technique in the clinical setting of the tissue augmentation procedures can provide the physician a reliable tool to define those filler-specific features in order to validate the anamnesis given by the patient.

According with each manufacturer's guidelines, permanent and non permanent fillers cannot be used in the same site, because of the risk of unknown interactions among diverse materials in a small space that could produce complications.

To be able to differentiate from a re-absorbable to a permanent implant before attempting further treatments can dramatically reduce complication rates and unfavorable results.

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Chapter 4

The utility of high frequency ultrasound in dermal fillers evaluation

Francesca R. Grippaudo MD, Mauro Mattei MD*

Plastic Surgery Unit, 2nd Medical Faculty, Sapienza University of Rome, S Andrew's Hospital, Via di Grottarossa 1035, Rome, Italy

*Radiology Dept., S Andrew's Hospital, Via di Grottarossa 1035, Rome, Italy.

Annals of Plastic Surgery 2011;67:469-473

Key words: High Frequency Ultrasound, Imaging, Dermal Filler, Complications

Abstract

Aim of this study is to describe the use of high frequency ultrasound to ascertain the site, quantity and type of filler injected in the soft tissue of the face , with respect to reliability of the procedure and the analysis costs.

Between December 2006 and August 2010 80 subjects, aged 25 to 65, who underwent facial filler augmentation, were submitted to high frequency sonography (HFUS).

Forty-two patients (22 after temporary filler and 20 after permanent filler) were healthy and satisfied of the treatment. Thirty-eight patients were seeking a consultation for filler related problems.

In 86,25 % of the patients the filler was known whereas in 13,75 % the nature of the filler injected was unknown.

Besides 4 patients, previously treated with temporary products, in which no foreign material was detected, HFUS consented in 97,5% of pts to identify and quantify the presence of a filler in the soft tissue. Moreover, it was possible to detect inflammatory reaction, often silent, granulomas, and recognise the presence of diverse fillers in the same area.

Ultrasonography has proved to be an useful, unexpensive, non-invasive tool for the identification of the site, quantity and often even nature of the filler injected.

Introduction

The use of fillers has grown substantially over the last ten years, generally providing good results. Many new materials are continuously introduced in the market for cosmetic tissue augmentation claiming to be temporary (collagen, hyaluronic acid), permanent (Hydrophilic Polyacrilamide gel – PAAG, Polymethylmetacrilates, Acrylic hydrogel

particles Polyacrilimmide gel) or long lasting (idroxyapatite, polilactic acid, DEAE Sephadex). All these products are claimed to be inert, non allergenic, well tolerated, non migrating and easily removable in the rare event of complication (1,3).

Fillers are effective in contrasting skin's natural aging process, but patients often seek multiple tissue augmentation procedures, often at yearly distance and from different physicians, to maintain a youthful appearance.

The use of diverse injectable substances for facial and body contouring is a growing problem when used by untrained persons, or when diverse fillers are used in the same area. Patients aren't always aware of the materials implanted in previous treatments, or may disguise that they have already had a treatment: this make difficult to safely perform further cosmetic procedures as required. Late severe complications may show up after the subcutaneous injection of permanent fillers (4), liquid silicone or with substances not intended for human applications (industrial silicone), (5). Even if this practice is condemned in many countries, it is still in use because of the ease in buying these products via internet, and because of the low cost compared to others fillers. High frequency diagnostic ultrasound has proved to be a useful tool for non invasive imaging of the healthy and pathologic skin and subcutaneous tissue (6), and has been shown proved to be a useful tool to discriminate among some temporary and permanent filler in healthy patients (7). It seemed logical to further investigate the filler detecting procedure in soft tissue with high frequency sonography (HFUS) to assess the minimum volume that can be identified and its correlation with physical examination, while analysing the procedure cost.

Materials and methods

For this study HFUS imaging data base of eighty patients who had tissue augmentation for cosmetic purposes with a dermal filler were

reviewed. Site of injection were the glabella (10), the lower lid (8), the zygoma (18), the jowls (6), the nasolabial folds (120) and the lips (82). Some patients received filler injection in more than one site. Patients were divided in two groups: group A was composed by 42 healthy and satisfied patients, of whom 22 treated by the senior Author 6 weeks to 3 months before the sonographic exam with temporary fillers for lip augmentation or nasolabial fold correction with collagen (Evolence™, ColBar Life Science, Israel) or hyaluronic acid (Restylane®, Q-Med ICT, Sweden). The filler volume ranged from 0,5 to 1 ml per injection site. The rest of group A was composed by 20 patients seeking a consultation for various cosmetic procedures with an history of permanent filler treatment performed elsewhere over a period of 6 months to four years before, all of them showing product proofs of identification (label or box): eight patients with Aquamid™ (Contura International, Soeborg, DK), six with Bio Alcamid™ (Polymekon, Brindisi, Italy), two with Matridex® (BioPolymer GmbH & Co, KG, Germany). In group A were included 4 patients reporting injection of liquid silicone. The volume of filler injected was impossible to estimate precisely, but the range of treatment varied from 1 to 3 injections per area.

Group B was composed by 38 patients seeking a consultation for filler related problems, all of them performed elsewhere over a period of 8 months to ten years before: of those 27 showed the label of the filler injected or a physician reference letter, 11 ignored the nature of the product (Table 1). Adding up the above-mentioned fillers, some of the patients of group B presented Gore-tex threads (WL Gore, Flagstaff,AZ) and Radiesse (BioForm Medical Inc, San Mateo, CA). The injected filler volume was impossible to identify precisely, but the range of treatments varied from 1 to 8 for each patient.

Complications consist in product migration, lumps, acute and chronic infection, pain (Table 2). Often multiple complication presented in the same patient.

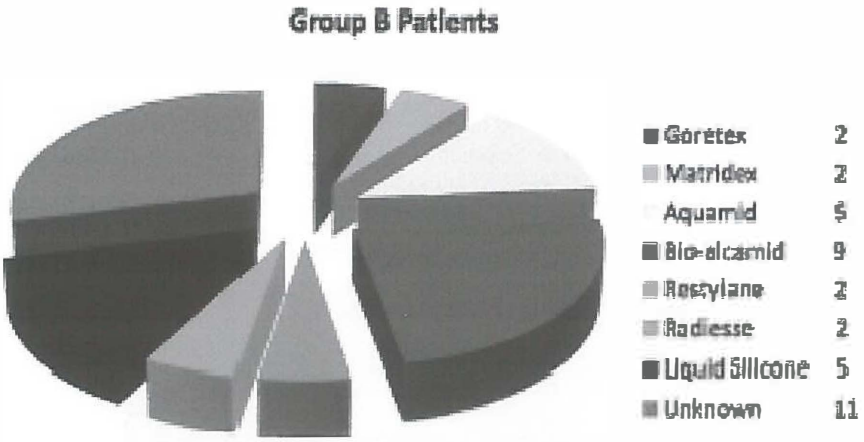


FIGURE 1. Products distribution in 38 patients showing filler-related complications. Eleven patients ignored the nature of the filler implanted. All treatments where performed elsewhere.

The physical examination of the sample was performed through inspection and palpation of every injection site searching for lump or deformity and the results were reported in each patient's chart.

All sample had the treated area, and in some case the full face, scanned using high-frequency ultrasound.

The exam was performed with a Hitachi H21 (Hitachi Medical Corporation, Tokyo, Japan), with a high-resolution probe 10-13MHz small parts.

Ultrasound gel (Aquasonic gel 100, Parker Laboratory, Fairfield, NJ,USA) was applied on the site to explore, and often a silicon gel pad (Aquaflex, Parker Laboratory, Fairfield, NJ, USA) was interposed between the probe and the skin.

Once the filler was detected the scan image was acquired and saved. Using the sonoCT software program it was possible to take measurements of the filler and soft tissues.

Results

In all the study population, with the exclusion of two subjects of Group A who had received 0,5 ml of collagen to nasolabial folds two months before the HFUS, and of two subjects of Group B who were treated with hyaluronic acid in nasolabial folds 2 years before, it was possible to clearly visualize the filler injected in the subcutaneous layer.

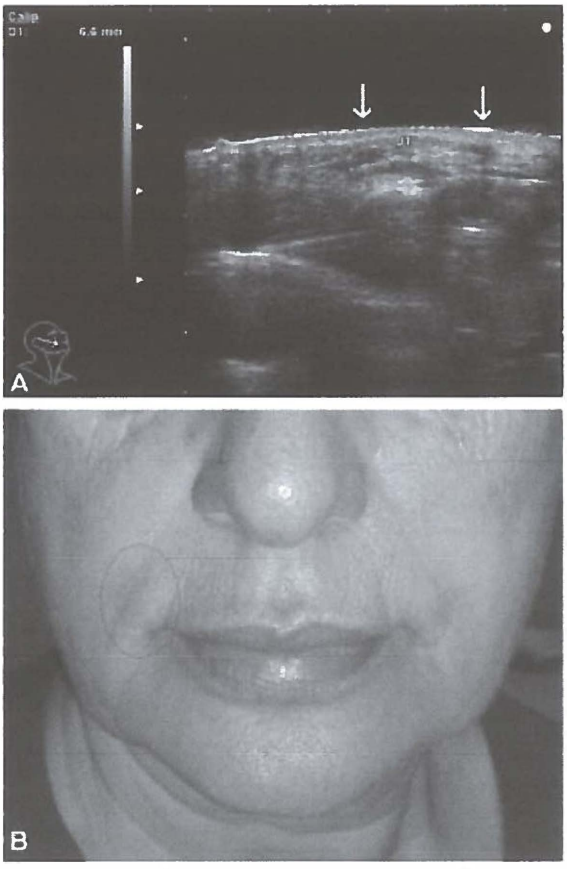


FIGURE 2. A, Collagen (Evolence) implant for right nasolabial fold augmentation, 11 weeks after the procedure. Arrows show well-defined regular hypoechoic masses in the subcutaneous tissue, without any signs of internal echoes. The Aquaflex pad was interposed between the probe and the skin. D1 indicates an implant size of 6.6 millimeters. B, The black oval over right nasolabial fold indicates the sonographic image of the implant. Physical examination was

Several scan were acquired to measure the implant, and the minimum volume detected by HFUS was of 1mm.

Sonographic image of Dermal filler, with the exclusion of silicone, is of a mass always having a distinct edge, within the soft tissue. The ultrasonographer could distinguish the temporary or permanent nature of the fillers in the sample population due to the different characteristics of the sonographyc patterns. In temporary fillers the mass appears anechoic or hypoechoic (fig. 2a, b), but it is not possible to distinguish between collagen and hyaluronic acid.

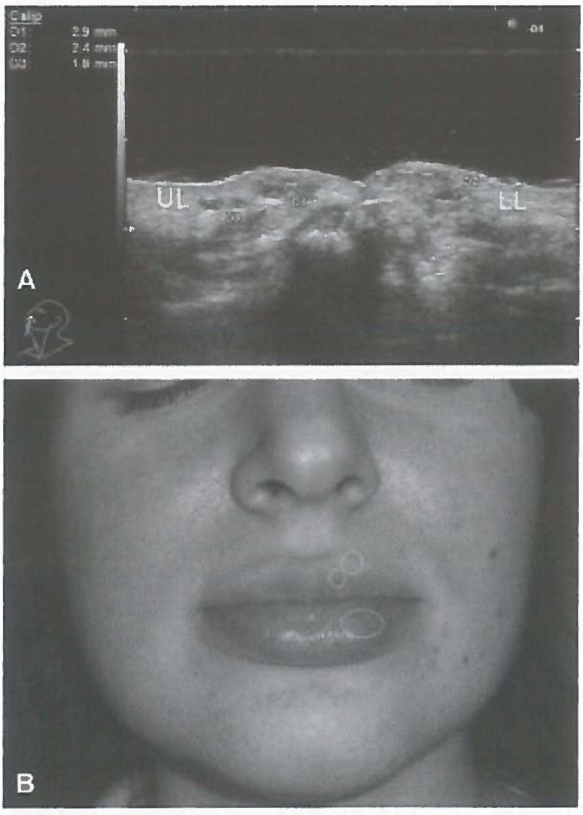


FIGURE 3. A, Aquamid implant for upper lip augmentation 2 years after the procedure. UL indicates upper lip, LL indicates lower lip. D1, D2, and D3 indicate small lumps size of hyperechoic image at HFUS. The Aquaflex pad was interposed between the probe and the skin. B, white circles indicate the small lumps detected with HFUS. A diffuse lips hardening was detected at physical examination.

Sonography of permanent fillers shows an hyperechoic contents (acrylic polymers gels) (fig 3a, b) or hypoechoic collection associated with internal foci of varying echogenicity (idroxyapatite, DEAE Sephadex) (fig.3a, b).

Gore-tex threads have a typical morphology of linear hypoechoic band of constant section (fig 4 a, b).

Liquid silicone shows a strong acoustic shadowing of scattered and reverberating echoes with well defined anterior margin and a posterior loss of details, with the typical appearance as a "snowstorm" (fig 5a, b).

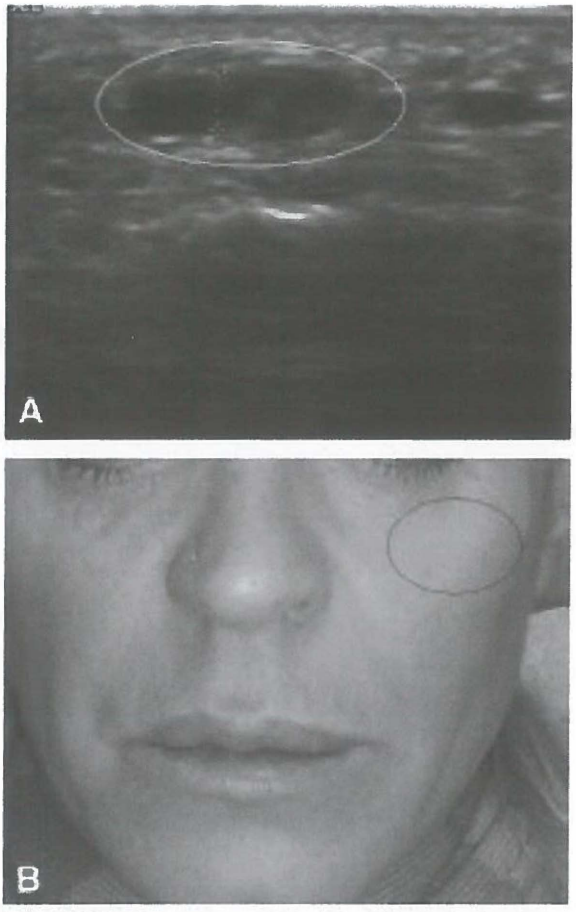
Sonography made it possible to detect the presence of different fillers in adjacent areas in three patients (fig 6a, b).

Granuloma was identifiable as an irregular lump of variable dimensions (range 1,8mm to several cm) without a distinct border form soft tissue and showing an irregular sonographic pattern (fig 7a, b). Fluid collections were visualized by the US as well. Patients with an history of chronic inflammation processes showed the presence of a hyperechoic wall of various thickness around the implant.

Adversely, only in 25% of group A patients, and in 78,9% of group B patients it was possible to palpate a lump or a diffuse hardening of the soft tissue.

The depth of the product in the soft tissue of the face varied from 2 mm (lip or lower lid) to 1,5 cm (cheek). The use of the gel pad made it possible to keep within the focus of the ultrasound machine the filler even in the first millimetre of skin.

The investigation time, from image acquisition to report printing, takes about 20 minutes and was reported by the patients as quick and comfortable.



URE 4. A, White oval encircles the Matridex implant for le
matic augmentation done 14 months after procedure.
ographic pattern is of hypoechoic image with internal foci
arying echogenicity. B, Black oval indicates the image de-
ed with HFUS. Physical examination was negative.

Discussion

Scarce reports appear in the literature showing the sonographic aspect of various dermal fillers, mainly to ascertain the cause of local complication (8).

In a previous study the Authors have described the use of HFUS to distinguish the temporary or permanent nature of a dermal filler in the healthy patient (7).

In this study on a bigger sample HFUS consented to appraise the actual location and the volume of a filler implanted in the soft tissue of the face. This aspect is useful when planning subsequent correction for cosmetic purposes, and represents as well a visual aid to demonstrate the "enhanced features" to the cosmetic patient.

Our findings show that temporary or permanent fillers appears as small mass with a neat margin from the soft tissue. Temporary fillers show a typical hypoechoic pattern, whereas permanent fillers composed by acrylic hydrogel (Aquamid™ and Bio Alcamid™) have an hyperechoic pattern surrounded by a wall that increases in thickness in case of inflammatory processes.

Matridex® and Radiesse® have a sonographic pattern in between temporary and permanent filler because appear hypoechoic but with denser areas inside. Goretex ® threads and liquid Silicone have a distinct pattern that makes their identification easy.

The injection of medical grade silicone for cosmetic purposes is now illegal in most countries in the world because of significant late reactions to silicone treatments, but its use was widespread in the past (9, 10).

The migratory stream of patients from regions were this practice is still used, as well as the illegal treatments often given misleading the patients makes HFUS a highly valuable tool in identify the presence of liquid silicone, as previous studies have shown (8,11), before treating a new patient.

Young et coll (12) have demonstrates the ability of HFUS to assess temporary filler implanted in the lip, and to obtain a clearer image a gauze pad was located in front of the teeth.

Our procedure differs from Youngs, because of a gel spacer, the Aquaflex pad, which was interposed between the probe and the skin when

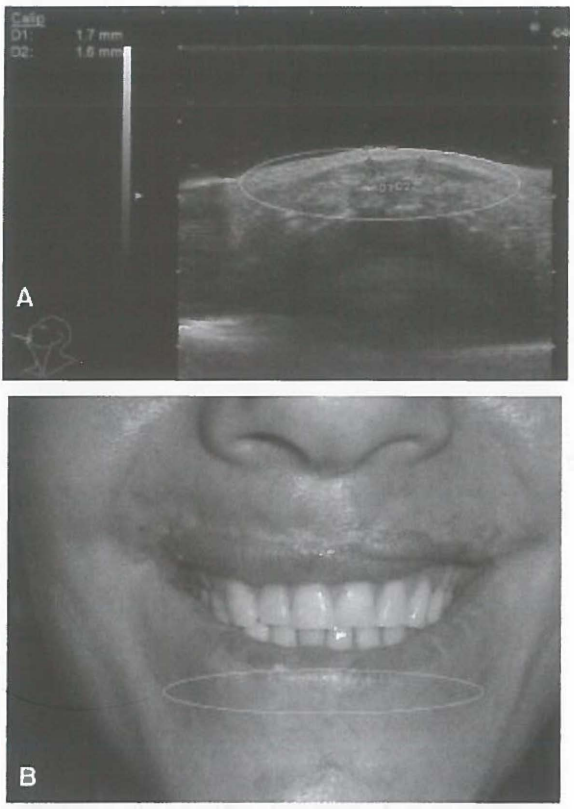


FIGURE 5. A, Gore-tex thread for inferior lip augmentation, 2 years after the procedure. White oval shows the thread images in subcutaneous tissue. The Aquaflex pad was interposed between the probe and the skin. B, white oval indicates the position of the Gore-tex thread in the lower lip, and coincide with sonographic image of the implant.

the filler was located very superficially (lip, lid, etc), to overcome the lack of resolution in the first 2 – 3 mm. Another advantage of the gel pad is that on an uneven surface as is the face, offers a better probe positioning.

This improvement consent to avoid any tissue compression, whilst providing a fixed 2 cm depth to make simpler visualize difficult near field areas and superficial structures. After this study it is possible to report that nature of the tested temporary fillers, if still present in the tissues, can be

always identified, because of their homogeneous hypoechoic pattern that do not elicit any sonographic sign of reaction in the surrounding tissues.

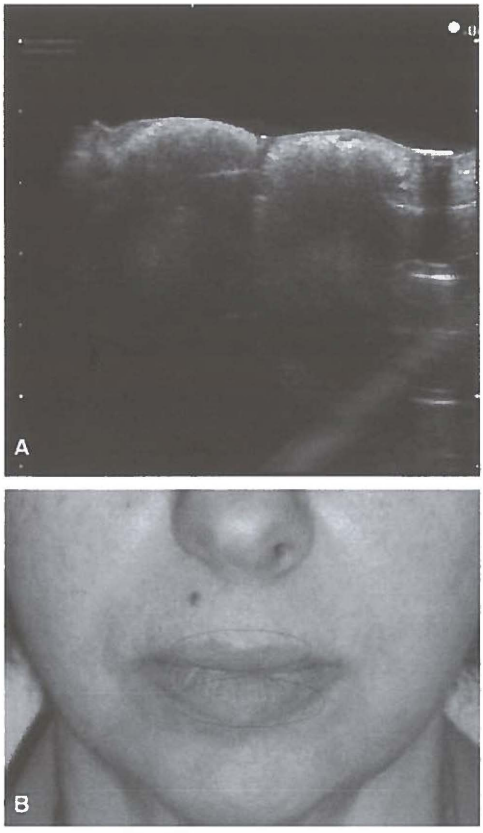


FIGURE 6. A, Liquid silicone for upper and lower lip augmentation 2 years after the injection. It is possible to visualize a strong echogenic noise, just below the vermilion, obscuring the surrounding soft tissue, with the typical "snowstorm pattern." The Aquaflex pad was interposed between the probe and the skin. B, black ovals indicate area submitted to HFUS. Physical examination detected diffuse lips induration.

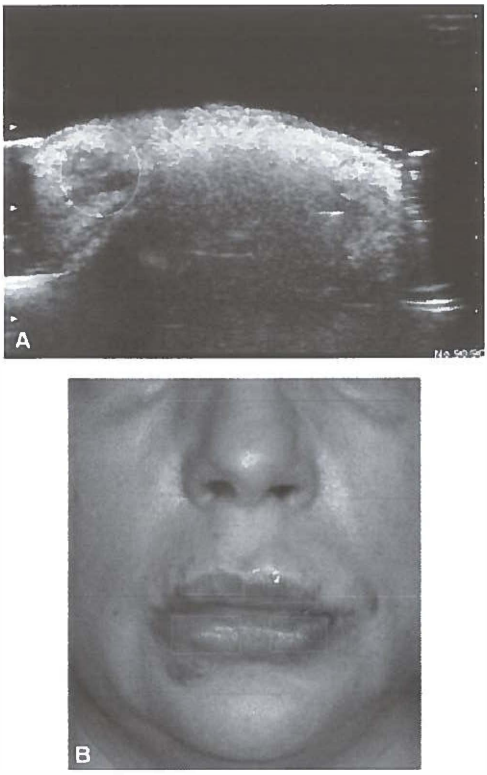


FIGURE 7. A, Liquid silicone injection in central part of the upper and lower lips performed 6 years before, acrylic polymer gel was injected at yearly distance in correspondence of oral commissures. Part of acrylic polymers gel, on the right side dislocates under the lower lip where is indicated by a white circle. It is possible to visualize the typical "snowstorm pattern" of the liquid silicone. The Aquaflex pad was interposed between the probe and the skin. B, white rectangles indicate the indurated area where liquid silicone was injected, while black circles indicate the acrylic polymers gel locations. Physical examination highlighted a diffuse perioral hardening, with multiple lumps.

Indrizzi er al. investigated the use of ultrasound imaging in detecting the modification of Bio Alcamid™ after its implant in soft tissues for reconstructive purposes (13) from 7 days to 36 months. They reported an image change from the anecogenous mass of recent implants only to

corpuscolated mass with ageing of the material. In our sample treated with Bio Alcamid™ we evaluated patients with older implants only, so far an anechoic image was never observed: this is probably due to the high water content of this product that is quickly reabsorbed after the injection. Although all of the patients in group A who received Bio Alcamid™ did not showed or reported any clinical sign of local pathology, the sonographic pattern of inflammations were sometimes detected.

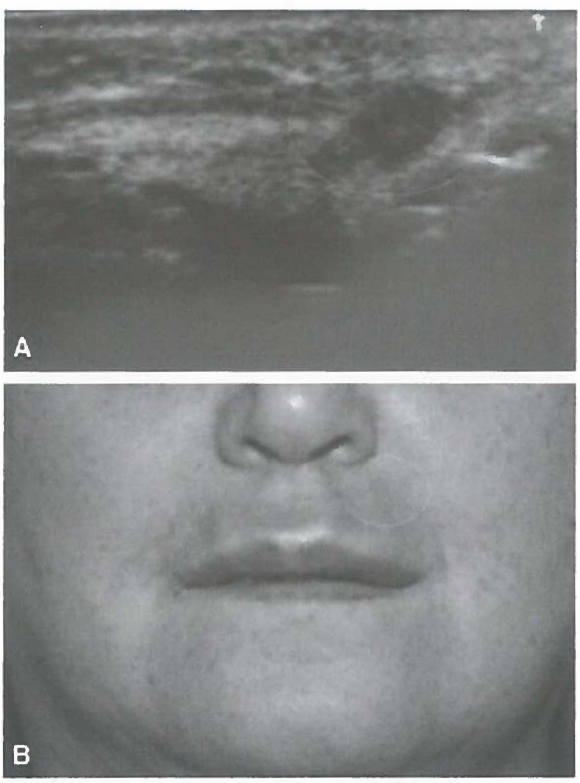


FIGURE 8. A, Granuloma of left nasolabial fold, 2 years after Bio-Alcamid injection. White circle indicates an area of irregular sonographic pattern without a distinct edge from healthy tissues. B, white circle indicates the corresponding area of the sonographic image. A hard lump was palpated in left nasolabial fold.

Within the cohort of 80 filler treated patients with 244 investigated areas, during the physical examination 66 clearly palpable lumps were identified, as well as 88 findings of diffuse soft tissue thickening, and 90

negative findings. Besides 4 patients whose negative findings are related to the scarce amount of the temporary filler implanted or to the time span between the injection procedure and the examination, with HFUS it was possible to highlight 240 implants. HFUS has shown to be a more sensible exam then palpation only in assessing filler permanence in soft tissue of the face.

HFUS is an ideal diagnostic instrument to evaluate complications as diffuse fibrosis, fluid collection or granuloma due to their typical pattern.

The exam was user friendly, quick, cost effective and very well tolerated by the patient. The learning curve for this kind of exam is estimated to be around 30 to 50 exams with diverse filler evaluation, which may need 3 to 6 months; since every country has different hardware costs and hospital wages we give an average exam cost in time needed to provide a diagnosis, which can be given by an experienced operator in approximately 20 minutes.

Conclusion

HFUS is a very useful technique and can precisely identify the location of the dermal filler its quantity within the soft tissues of the face. As shown from our results, filler sonographic localization and measurement was possible in 97,5% of the cases.

In this retrospective analysis it is not proposed that HFUS replace the clinical examination and patient history before performing filler injections procedure, but this technique can add valuable information with patient that could have been already treated with a known or unknown filler.

Interactions among diverse fillers are still under investigation, and manufacturer's guidelines warn against the use of different materials in the same site, because of the risk of complications.

To be able to detect the presence of an implant and its identification in absence of medical documentation, before attempting further treatments can dramatically reduce complication rates and unfavorable results.

Introducing this technique in the clinical setting of the tissue augmentation procedures can provide the physician a cost effective, quick and reliable tool to define those filler-specific features in order to validate the anamnesis given by the patient.

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Chapter 5

MRI in the assessment of facial dermal fillers: a pilot study

Marco Di Girolamo[1], Mauro Mattei[1], Alberto Signore[2,3], Francesca R. Grippaudo[4]

[1]Radiology Unit, [2]Nuclear Medicine Unit, [4]Plastic Surgery Unit, Faculty of Medicine and Psychology, "Sapienza" University of Rome, Italy.

[3]Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, The Netherlands.

Radiology 2013 (submitted)

Key words: Dermal filler, MRI, granulomas, imaging

Abstract

Purpose: To ascertain by MRI the presence of filler injected in facial soft tissue and characterize complications with contrast-enhancement.

Materials and Methods: In a first series of 19 patients (10 after temporary and 9 after permanent filler) we investigated if MRI was able to detect the presence and nature of the filler. Following the results of first group we enrolled 26 more patients with filler-related complications, clinically diagnosed (pain, inflammation, ulcers, edema, redness, lumps) and we evaluated if contrast-enhanced MRI was able to characterize the lesion. TSE-T1-weighted, TSE-T2-weighted, fat-saturated TSE-T2-weighted and TIRM scans on axial and coronal plane were performed. In filler-related complications, fat-suppressed TSE-T1-weighted scans were performed after i.v. administration of Gadolinium-DOTA. In group 2 patients, a skin biopsy was performed in patients with soft tissue enhancement and in 5 patients without any enhancement but who did not improve after antibiotic therapy. Fisher's exact test was used for statistical analysis. In complicated cases, cervical lymph node enlargement was evaluated (longitudinal axis>10mm).

Results: In group 1 patients MRI always identified and quantified the filler in soft tissue. Temporary dermal fillers appeared as hypointense spots in T1-weighted and hyperintense in T2-weighted images. Permanent fillers appeared as hypointense spots in T1-weighted images while the signal intensity in T2-weighted images varied. In group 2 patients with complications, T2-weighted images showed hyperintense lesions only in 11 patients and hypointense lesions only in 6 and both hyperintense and hypointense lesions in 9 patients. A positive subcutaneous contrast-enhancement was detected in 9 patients over 26. Skin biopsy in these 9 patients confirmed the presence of an inflammatory granulomatous reaction.

Five of the 17 patients without contrast-enhancement also performed a skin biopsy with a negative finding for granulomas. Fisher's exact test found a significant correlation ($P<0.001$) between subcutaneous contrast-enhancement and granuloumatous reaction. Cervical lymph nodes enlargement was found in 16 complicated patients (levels IA, IB, IIA, IIB).

Conclusion: MRI is a useful and non-invasive tool for anatomical localization of facial dermal filler and i.v. Gadolinium administration is advised in complicated cases for better characterization of the lesion although lack of specificity for infected lesions.

Introduction

Cosmetic tissue augmentation and correction of skin depressions using injectable material is not a new concept. In the last decade many new materials were introduced in the market claiming to be permanent, inert, non allergenic, well tolerated, non migrating and easily removable in the rare event of complications (1,2).

Dermal fillers differ in composition and can be classified according to their persistence in the soft tissue. *Temporary dermal fillers* are made by collagen and hyaluronic acid (HA), which are reabsorbed by the body over a period of 6-12 months (3). *Long lasting filler* are made by Poly-L-lactic acid (PLLA) (Sculptra®) (4), or synthetic calcium hydroxyapatite microspheres (CaHA) suspended in sodium carboxymethylcellulose gel (Radiesse®) (5), or dextran molecules-Sephadex and hyaluronic acid (Matridex®), which stay for 2-3 years in the tissue prior to degradation (3). *Permanent dermal fillers* might be made by polymethylmethacrylate (PMMA) with or without collagen as a vector (Artecoll®, Metacrill®) (6), by polyacrylamide hydrogel (PAAG) (Aquamid®, Royamid®, Formacryl®) (7), by polyalkylimide (PAIG) (BioAlcamid®) (8), by acrylic hydrogel (AH) (Dermalive®) (9), by silicone particles suspended in a polyvinylpirrolidone carrier (Bioplastique®) (10). All

these substances are designed to be encapsulated by the body's own connective tissue where they remain forever (11).

The use of liquid silicone injections for cosmetic use has been banned by several countries, but it is still seen in elderly patients or patients from non-Western countries (12, 13).

Despite the minimally invasive nature of the dermal fillers, there are some complications related to them (14). Common *short term complications* usually occur within the first few weeks after treatment and include bleeding or bruising, redness at the site of injection and oedema, usually resolving spontaneously in few days. There is always a risk of a technical error from overcorrection or because the product is injected in the wrong site.

The *long-term complications* (after six months from the treatment) are the formation of foreign body abscesses and granulomas, product migration, and cross-reactions among different products injected in near-by sites, producing diffuse oedema, skin discoloration and lumps (15, 16, 17).

Comprehensive epidemiologic data on complication's rate related to dermal fillers treatments are not available, due to the multitude of fillers in the world market, the small number of national registries and, when present , the voluntary nature of adverse event reports (18). Overall complication 's rate of dermal fillers as reported in literature and based mainly on case reports papers varies from 0,01% after PMMA to 52% after PLLA, with the other fillers within this range (19).

Patients seeking facial cosmetic augmentation are not always aware of the nature of the material used in previous sessions given by different physicians, in absence of palpation reliefs. In these patients, prior to the injection of any further filler, in order to avoid complications, high frequency ultrasound (HFUS) has proved to be a useful tool to detect these dermal fillers in soft tissues (20-22).

MRI is a diagnostic technique that has high intrinsic contrast allowing an evaluation of soft tissues without any exposure to ionizing radiation but

with higher costs in comparison with HFUS. MRI is a multiplanar and multiparametric tool that obtains a good spatial evaluation concerning the actual site of any foreign body with respect to the anatomical landmarks (23).

The aim of this study is to investigate the role of MRI to detect dermal filler injected in the facial soft tissues for cosmetic purposes and to assess any complications related to this procedure. After its valuable role in inflammatory reactions (24), it seemed logical to investigate the application of intravenous administration of paramagnetic contrast media in the evaluation of inflammatory complications after filler injection.

Materials and methods

Patients selection:

For group 1, 19 consecutive patients referred to plastic surgery unit after temporary or permanent dermal filler injection into the face for cosmetic purposes were enrolled between January 2009 to March 2010. None of them had any contraindications to the MRI study. Ten patients received an injection of temporary dermal fillers from 4 to 7 months preceding the clinical evaluation and had no clinical evidence of complications. The remaining 9 patients received injections of permanent dermal fillers from 9 months to 10 years preceding the clinical evaluation and had no clinical evidence of complications.

For group 2, we recruited 26 patients with local complications (erythema and swelling of different intensity and duration) after a dermal filler treatment of known (20 pts) or unknown (6 pts) nature in their facial soft tissues, performed from 3 to 12 years before the consultation. Twelve patients had received inoculations of different fillers.

All patients underwent MRI examinations of the head and neck.

The study protocol was approved by the Local Ethical Committee (Prot. C.E.: 554/2012) and all the patients signed an informed consent.

MRI:

All the MR examinations were performed with a 1.5 Tesla superconductive unit (Sonata, Siemens, Germany) using head and neck coil.

Axial and coronal TSE T1-weighted (acquisition parameters: TR: 600 ms; TE: 11 ms; ETL: 5) and T2-weighted scans (acquisition parameters: TR: 3600 ms; TE: 108 ms; ETL: 19) were performed with a slice thickness of 3 mm.

TSE T2-weighted axial scan with fat saturation were performed (acquisition parameters: TR: 3600 ms; TE: 108 ms; ETL: 19) and subsequently Turbo Inversion Recovery Magnitude (TIRM) sequences on axial plane with 3 mm slice thickness were obtained using the following acquisition parameters: TR: 9120 ms; TE: 67 ms; TI: 150 ms.

In group 2 only, fat suppressed TSE T1-weighted axial and coronal scans were performed after the I.V. administration of Gadolinium-DOTA (Dotarem; Guerbet; France), with the dosage of 0.1 mmol/kg. The MR acquisition started 2-3 minutes after the i.v injection of contrast media.

Image interpretation, skin biopsy and statistical analysis:

MR images were interpreted as follow:

1) qualitative evaluation on the filler signal intensity on T1 and T2-weighted images in comparison with subcutaneous fat tissue (hyperintese, isointense or hypointense signal);

2) evaluation of the quantity and site of filler injection considering as anatomical landmarks mandible, lips, nose, zygomatic region, orbits and glabella;
3) qualitative analysis concerning the presence or absence of contrast-enhancement at the level of subcutaneous fat tissue in complicated patients only (group 2) reported as positive or negative;
4) detection of enlarged cervical lymph nodes. Cervical lymph node enlargement was assessed and when positive (lymph node longitudinal axis superior to 10 mm) their level were established considering the classification of the American Academy of Otolaryngology and Head and Neck Surgery (AAO-HNS) and the American Joint Committee on Cancer (AJCC) (25).

The MR examinations were evaluated by a blinded radiologist (MDG) with experience in head and neck pathologies who was unaware of the nature of filler injected but was conscious of the complicated cases evaluating the contrast-enhanced images.

Cutaneous biopsy was performed by plastic surgeon (FRG) in all the patients showing positive enhancement after the i.v administration of Gadolinium-DOTA as well as in 5 patients without any enhancement.

Complicated cases with negative contrast enhancement received antibiotic therapy prescription, as previously reported (26). As stated by our Local Ethical Committee only the patients without any clinical improvement after three weeks of therapy underwent subsequent skin biopsy.

Statistical analysis concerning the relationship between subcutaneous contrast enhancement after the injection of Gadolinium-DOTA and histological specimen was done with the Fisher Exact Test. Data were analyzed using statistical software (Inc. Sigma Plot Version 12.0; Systat Software).

Table 1

PTS	Type of filler	T2-w. signal intensity	Sites of injection	Lymph node enlargement and site	Contrast chancement after Gadolinium	Occasional findings
Female	HA	Hyper	Zigomas Nasolabial folds	No	No	Chronic ischemic cerebral gliosis
Female	HA	Hyper	Zigomas Nasolabial folds	Bilateral IB, IIA, IIB	No	Left face Skin redness and blisters
Female	HA	Hyper	Nasolabial folds	No	No	
Female	HA S	Hyper Hypo	Nasolabial folds Lips	Right IB, Bilateral IIB	No	
Female	HA PAIG	Hyper	Lips	Bilateral IB	No	
Male	PLLA HA	Hypo Hyper	Glabella Nasolabial folds	Bilateral IB	No	
Female	HA PAAG Unknown	Hyper Hyper Hypo	Cheeks Lips Zygomas	Bilateral IIA, IIB	Yes	Right Skin ulcer Lupus and lichen
Female	PAAG	Hyper	Lips	Bilateral IIA, IIB	Yes	Left frontal Meningioma
Male	PAAG	Hyper	Glabella	No	No	Post traumatic malacic frontal area
Female	PAAG S HA	Hyper Hypo Hyper	Zigoma sx,lips Zigoma dx, chin Zygomas	Bilateral IB, IIA, IIB	No	**Dental implant MR artifacts**
Female	CaHA HA	Hypo Hyper	zygomas	No	No	**Dental implant MR artifacts**
Female	PAIG C	Hyper Hyper	Zygomas and cheeks Lips	Bilateral IIA	No	**Dental implant MR artifacts** Left temporal

						arachnoid cyst
Female	PAIG	Hypo	Zygomas and cheeks	No	Yes	Right dental apical granuloma
Female	HA PAIG	Hyper Hyper	Glabella and Nasolabial folds Zigomas, Lips and Cheeks	Bilateral IIA, IIB	No	**Dental implant MR artifacts**
Female	S	Hypo	Lips	No	No	
Female	S HA	Hypo Hyper	Lips Zigomas and Nasolabial folds	No	No	
Female	HA AH	Hyper Hypo	Nasolabial folds Lips and Glabella	Bilateral IIA	Yes	
Female	Bioplastique AH Unknown	Hyper Hypo Hypo	Nasolabial folds Zigoma Lower lip	Bilateral IA, IB, IIA, IIB (26mm)	No Yes No	
Female	AH	Hypo	Nasolabial folds, Lips and Glabella	Bilateral IIA, IIB	Yes	
Female	AH	Hypo	Lips	No	No	
Female	Unknown Unknown	Hyper Hyper	Lips	Bilateral IIA, IIB	No	
Male	Unknown	Hyper	Zygomas	No	Yes	
Male	Unknown	Hyper	Nasolabial folds	Bilateral IIA	Yes	
Female	Unknown	Hypo	Lips	Bilateral IB, IIA	No	
Female	Unknown	Hypo	Nasolabial folds	Bilateral IIA, IIB	Yes	
Female	Unknown Unknown	Hyper Hypo	Nasolabial folds	No	No	

Legend to Table 1:

HA= Hyaluronic Acid

C= Collagen

S= Silicone

PAAG= Polyacrylamide gel

PLLA= Poly-L-lactic acid

PAIG= Polyalkylimide gel

PMMA= Polymethyl-methacrylate micro-spheres

CaHA= Calcium Hydroxylapatite

Bioplastique= Silicone and Polyvinilpirrolidone

AH = Acrylic hydrogel particles, copolymer of 40% hydroxyl-ethyl-methacrylates HEMA and ethyl-methacrylate EMA and HA 60%.

Table 1: List of group C patients with local complications after facial fillers injection; this list describes sex, type of filler and sites of injection, signal intensity on T2-weighted images, lymph node enlargement, contrast enhancement after I.V. administration of Gadolinium-DOTA and occasional findings.

Results

All MR examinations were completed within 30 minutes without any patient discomfort or claustrophobia. MRI detected dermal filler presence in all patients, even when the clinical evaluation was negative. Three patients presented ferro-magnetic artifacts on some MR images due to the presence of dental implants, that partially impaired the diagnostic results of the exam.

MRI always clearly demonstrated the site of dermal fillers, allowing its precise anatomical localization, visualizing the anatomical landmarks (mandible, lips, nose, zygomatic region, orbits and glabella) on axial and coronal scans.

MR examination allowed the filler measurement, assessing its extent and depth in facial soft tissue of the face, with minimal size detected being 2 mm.

Patients in group 1, with temporary fillers, we observed liquid rounded droplets. HA and collagen appeared as multiple spots hypo-intense

on T1-weighted images and hyper-intense on T2-weighted images because of their water content (Fig. 1). In patients with permanent fillers, these appeared as a hypo-intense spots on T1-weighted images while the signal intensity on T2-weighted images was variable.

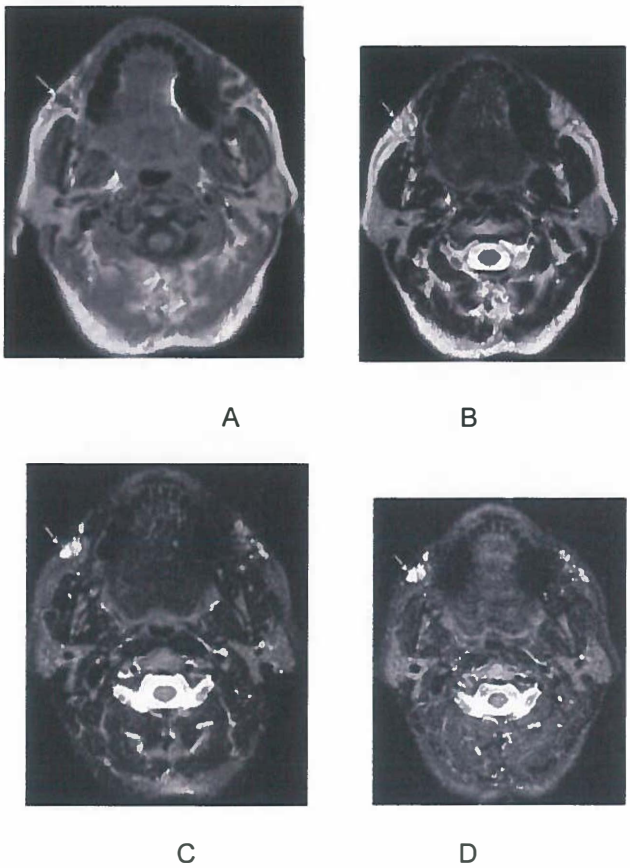

Fig. 1 (A, B, C, D): Group A patient with temporary dermal filler (HA) in zygomatic region and naso-labial folds. On axial FSE T1-weighted scan (TR: 600-800 ms, TE: 11 ms, ETL: 5) (A) HA appears with a hypointense signal (white arrow), while on axial FSE T2-weighted scans with or without fat saturation (TR: 2750 ms, TE: 108 ms, ETL: 19) (B and C) and TIRM acquisitions (TR: 9000 ms, TE 67 ms, TI 150 ms, ETL: 11) (D) HA appears with a homogeneous hyperintense signal (white arrow).

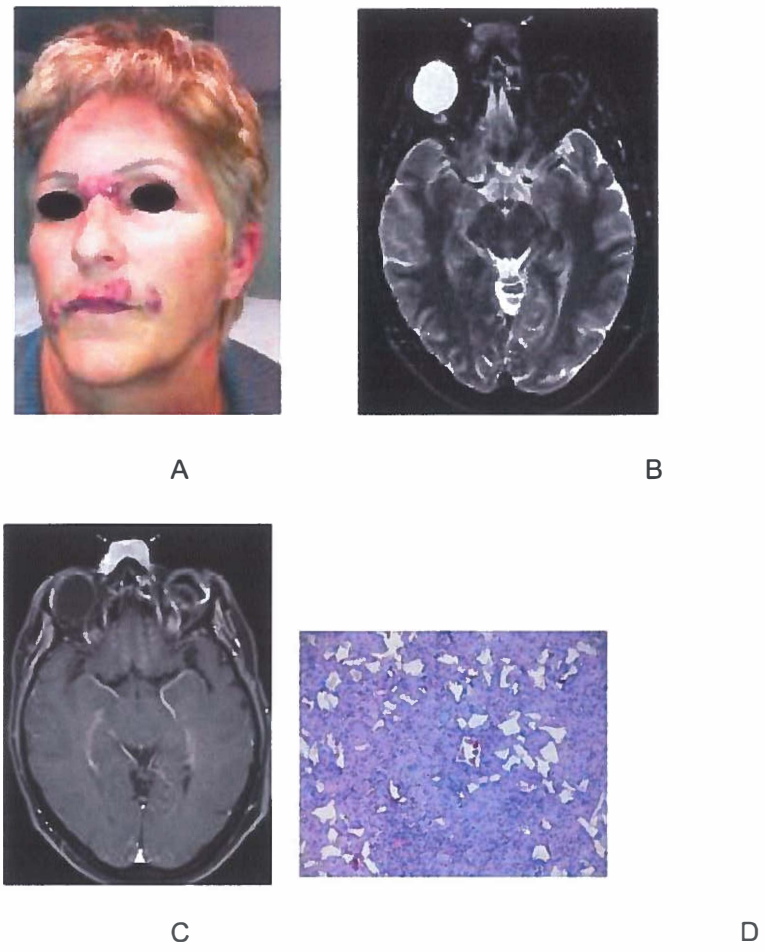

Fig. 2 (A, B, C, D): Group C patient with temporary dermal fillers (HA) injected 7 months previously, with lumps at the level of superior lip and glabella (A). The lumps showed hyperintense signal on TIRM acquisitions (TR: 9000 ms, TE 67 ms, TI 150 ms, ETL: 11) (B) (white arrows) and a strong contrast-enhancement on TSE T1-weighted fat saturated acquisition (TR: 487 ms, TE: 11ms, ETL: 5, TI= 150 ms) after the I.V. administration of Gadolinium-DOTA (C) (white arrows) on the same axial plane at the level of the glabella. Histological specimens stained with H+E (D) showed multiple spaces, optically empty or with material, surrounded by multinucleated giant cells (little white arrows) and by hystiocytes, forming some foreign body granulomas.

The T2-weighted signal was hyper-intense in five patients (3 had the injection of Aquamid® and 2 of Bioalcamid®) and hypo-intense in four patients (2 had the injection of silicone and 2 of Dermalive®).

In group 2 (Table 1) on T2-weighted images fillers appeared with hyper-intense signal intensity in 11 pts, hypo-intense signal intensity in 6 pts and in 9 patients images showed different signal intensity (both hyper-intense and hypo-intense lesions) due to different dermal fillers in the same patient.

After the injection of Gadolinium-DOTA, 9/26 patients (34.6%) presented areas of enhancement of the facial subcutaneous fat tissue suggesting the presence of an inflammatory/infective reaction. All 9 patients were therefore treated with antibiotics. Skin biopsy ascertained the presence of an inflammatory granuloma at the level of the enhanced area but not a clear infection (Fig 2, 3 and 4). In 5/17 patients with chronic complications, but without any Gd-enhancement, and without clinical improvement after antibiotic therapy, a biopsy did not demonstrate the presence of a granuloma but fibrotic tissue.

Fischer's exact test found a significant correlation ($p<0.001$) between facial subcutaneous contrast enhancement and granulomatous reaction detected by skin biopsy in complicated cases. The Fischer Exact Test considered only 14 patients who performed skin biopsy, 9 patients with subcutaneous contrast-enhancement and inflammatory granulomatous reaction and 5 patients without contrast enhancement and no histological finding of granuloma.

MRI detected in 17/26 patients (65.3%) cervical lymph nodes enlargement. The enlarged lymph nodes had a longitudinal axis superior to 10 mm (27). The lymph node level was IA in 1 patient (bilateral), IB in 7

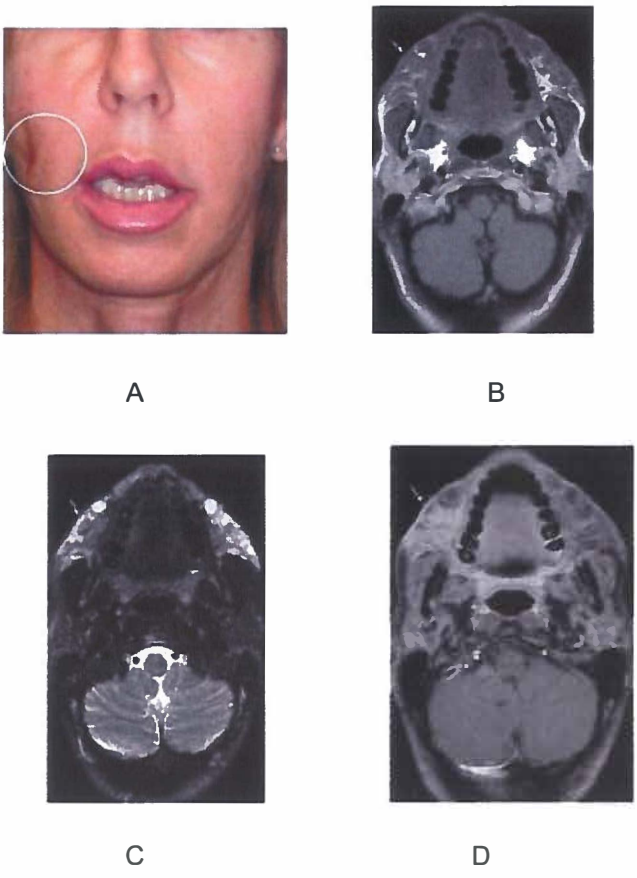

Fig. 3 (A, B, C, D): Group C Patient with cutaneous fistula in right zygomatic region (white circle) (A). MRI shows a diffuse deep fat tissue hypointense signal (white arrow) on TSE T1-weighted axial scan (TR: 600-800 ms, TE: 11 ms, ETL: 5) (B) while TSE T2-weighted axial scan (TR: 2750 ms, TE: 108 ms, ETL: 19) shows both hyperintense and hypointense spots (white arrow) (C) in right zygomatic region. TSE fat-saturated T1-weighted axial scan on the same plane (TR: 487 ms, TE: 11ms, ETL: 5, TI= 150ms) (D) performed after the I.V. injection of Gadolinium-DOTA shows widespread contrast enhancement of the subcutaneous fat tissue of the right zygomatic region (D) and a subsequent skin biopsy demonstrates a diffuse granulomatous inflammatory reaction.

(bilateral in 6 and mono-lateral in 1), IIA in 13 (always bilateral) and IIB in 10 patients (always bilateral) (Table 1).

The largest lymph node had a longitudinal axis of 26 mm and this patient had the involvement of IA, IB, IIA and IIB levels and had facial contrast enhancement in one of the sites of filler injection.The enlarged lymph nodes had always a longitudinal and axial axis ratio superior to 2 and never showed the same signal intensity of injected subcutaneous filler. In 2 patients having received silicone injection, no silicone was detected with MRI in enlarged lymph nodes. Lymph nodes never showed Gd-enhancement and were interpreted as inflammatory reactions.

MRI also allowed the detection of associated pathologies in five patients (1 frontal meningioma, 1 temporal arachnoid cyst, 1 chronic ischemic cerebral gliosis, 1 frontal area of malacia caused by a previous head trauma and 1 apical dental granuloma).

Discussion

Dermal filler related complications are a frequent pathology (14), often presenting several years after original cosmetic treatment. Because of the time span between the treatment and the complication, it is a common situation to deal with patients who don't remember the filler they had received; don't have the product leaflet; have lost contact with the physician that performed the treatment.

Knowing the site, size and the nature of the filler offers better chances to appropriately treat the complication.

CT scan has been proposed as a valuable tool in the evaluation of dermal filler (28) but in our opinion this diagnostic technique has the disadvantage concerning the ionizing radiation exposure to critical organs as crystalline lens.

HFUS is a reliable, diffuse and economical diagnostic tool useful in evaluating the site, the extension and the amount of dermal fillers injected. With this diagnostic procedure it is possible to ascertain the temporary or permanent nature of the product as well as suggest the diagnosis of granuloma (20, 21). The disadvantages of this technique are the lack of certain anatomical landmarks in the evaluation of the diagnostic images by the plastic surgeon, and the absence of consolidated criteria to diagnose inflammatory reaction.

Moreover HFUS is an operator dependent investigation that does not allow a second opinion in the evaluation of the diagnostic images. Therefore the HFUS evaluation, in controversial cases, may require the collaborative presence of both radiologist and plastic surgeon during the exam. Nevertheless, HFUS is often the first line diagnostic exam to be performed in patients having had filler injection because of the high availability. However considering the limits of HFUS, MRI could be proposed as the second line diagnostic exam, even though it has higher costs and reduced availability. The advantages of MRI are based upon its ability to provide excellent soft tissues evaluation due to the possibility of obtaining multi-parametric diagnostic images (23).

In our study TSE T1- and T2- weighted axial and coronal scan were used, with a total acquisition time of 20 min. The only drawback encountered was the reduction of contrast-to-noise ratio between the hyperintense subcutaneous fat tissue and the hyperintense filler on TSE T2-weighted images. This particular problem can be minimized using particular fat saturation acquisitions that null the subcutaneous fat tissue's signal so that the signal from other tissue is more conspicuous.

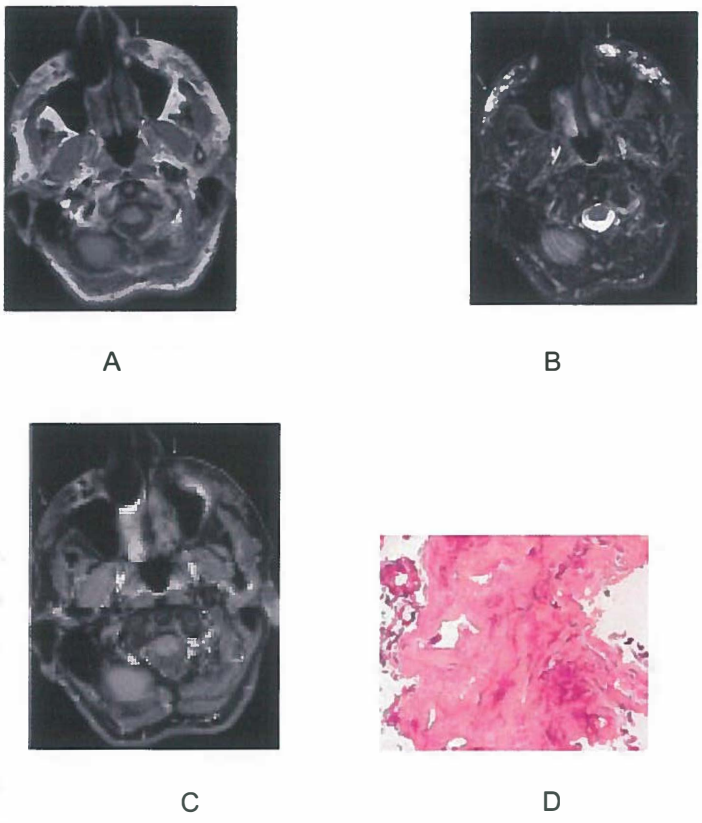

Fig. 4 (A, B, C, D): Group C patient with permanent dermal filler (PAIG) on both nasolabial folds and zygomatic region evaluated with TSE T1-weighted (TR: 600-800 ms, TE: 11 ms, ETL: 5) (A) and TSE T2-weighted fat saturated (TR: 2750 ms, TE: 108 ms, ETL: 19) (B) on the same axial scan (white arrows). After the I.V. administration of Gadolinium-DOTA no areas of contrast enhancement were detected on TSE T1-weighted fat saturated axial scan (TR: 487 ms, TE: 11ms, ETL: 5, TI= 150ms) (C) (white arrows). A subsequent skin biopsy and histological speciment stained with H+E (D) showed an amorphous material with collagen fibers without any inflammatory infiltration.

There are various techniques for achieving fat saturation with MRI (29). All techniques for fat suppression are based on the fact that - due to

the different chemical environment – hydrogen nuclei in water and in fat-tissue have different values for some MRI-relevant parameters, mainly the relaxation time and the resonance frequency (chemical shift). The most common method to achieve fat saturation is by applying a narrow band frequency selective RF pulse at the beginning of any sequence and following it immediately with a spoiler or crusher gradient that shifts the net magnetization vector of fat, so that it has no longitudinal magnetization at the beginning of the MR acquisition. This method was used in our experience on fat-saturated T2-weighted and on contrast-enhanced fat-saturated T1-weighted acquisitions. The second technique for obtaining fat saturation is the use of an inversion-recovery pulse to null the signal from fat. TIRM sequences are particular T2-weighted Inversion-Recovery acquisitions that are more efficient for nulling the signal from fat and in our experience allowed an optimal detection of dermal fillers within the subcutaneous fat tissue. This kind of acquisition is used also to null the signal from silicone that has a TI of 150 ms (30).

In the past, scattered reports appeared in the scientific literature proposing MRI in the evaluation of cosmetic filler (7, 28, 31, 32), but the increase of these cosmetic procedures and subsequent complications in the soft tissue of the face, requires the improvement of the application of this diagnostic modality.

Our study confirmed that HA appeared with an hyperintense signal on T2-weighted images as reported by previous study (31, 32), in which MRI was performed four times on each patient. In these studies the signal intensity of HA on T2-weighted images progressively decreased with time, due to product re-absorption. In our study, MR examination was performed just once on each patient and therefore it was impossible to demonstrate the signal intensity variations on T2-weighted images.

Bello et al. (7) reported a MRI assessment of polyacrylamide gel, implanted in rabbit ears showed no filler dislocation and an absence of inflammatory reaction after seven months follow-up. Our MRI findings

showed regional lymph node enlargement in 3 out of 4 patients with polyacrylamide gel filler and a subcutaneous contrast enhancement in 2 of those patients (Table 1). MRI detected a dislocation of polyacrylamide gel filler in the only patient without any other MRI pathological finding.

Moreover MRI, without any exposure to ionizing radiation, offers the plastic surgeon a spatial visualization on axial and coronal scans, concerning the site and the extension of the filler with respect to the anatomical landmarks and this result is not allowed by US.

MRI has an important role as a diagnostic tool in patients with complications after the injection of dermal fillers. MRI is a diagnostic modality that can accurately identify the presence of foreign material in the soft tissues and detect soft tissue inflammation in vivo as already shown by Paajaneen et al. (24).

The contribution of the present study statistically demonstrates that the gadolinium-enhancement of soft tissue observed in complicated cases after filler injection is a pathognomonic sign of a granulomatous reaction, excluding all the other complications. This is the first time that this correlation is reported and this finding is fundamental in medical care planning (Table 2) in case of filler complication. A previous study by Kransdorf et al. (33) reported a diagnosis of granulomatous inflammatory reaction based on the soft tissue enhancement after the I.V. administration of a paramagnetic contrast agent in case of subcutaneous granuloma anulare.

HFUS cannot diagnose certain granulomatous inflammatory responses after filler injection and therefore the higher costs of MRI are justified. The diagnosis of severe granulomatous reactions after filler injection for cosmetic purposes is mandatory for the subsequent treatment planning and can provide evidence if needed for legal action.

MRI allows filler characterization and evaluation of adjacent tissue modification after their in-vivo injection, especially using T2-weighted acquisition as shown by Gensanne et al. (31). In fact, the signal intensity of dermal fillers on T2-weighted images could be different, within the same

Table 2

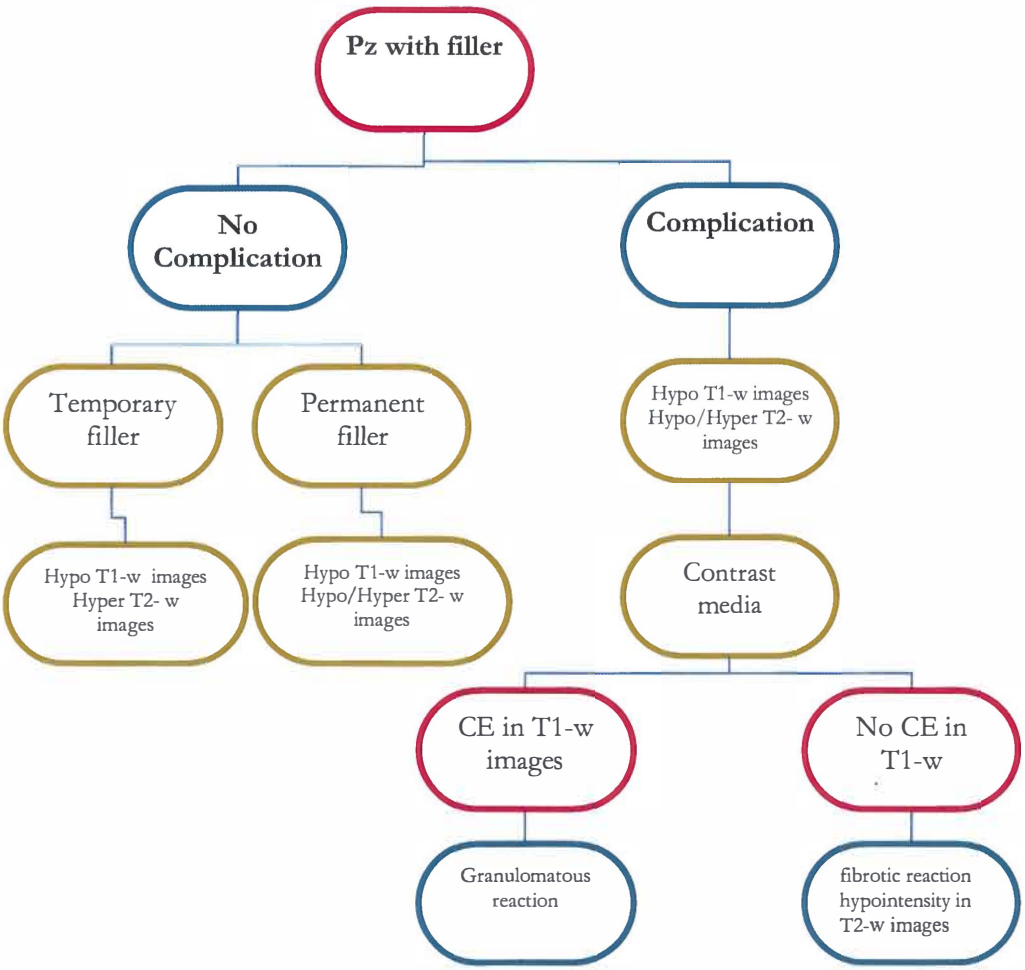

Table 2: Description of the proposed diagnostic MRI pathway in patients with facial dermal filler in normal and complicated cases.

subject, considering the injection of different products in different periods and the possible granulomatous inflammatory or fibrotic reaction. The filler appeared with a hypo-intense signal on T2-weighted acquisition in cases of fibrotic or granulomatous response. In such situations the use of paramagnetic contrast media is mandatory to differentiate fibrosis vs granulomatous reaction. In fact, fibrosis does not show any significant enhancement after I.V. administration of paramagnetic contrast media.

One report by Feeney (34) demonstrates an inflammatory reaction related to hydroxylapatite dermal fillers using FDG PET/CT and MRI in neoplastic patients who received filler injection after treatment. Feeney related facial subcutaneous intense FDG uptake associated with the presence of high attenuation material (600-700 HU) in the five patients evaluated by PET/CT, with a mild enhancement on the post-gadolinium sequence in only one patient evaluated by MRI, describing inflammatory reactions in the site of filler injection.

Recently, scintigraphy with radiolabelled WBC was found to be the most accurate method for diagnosing infection in patients with long-term dermal filler complications (26) and indeed the main limitation of MRI is the difficulty to differentiate between an inflammatory granuloma and an infected lesion. In case of clinical suspicion of infection or for better exclusion of an infective process (35) the scintigraphy with radiolabelled WBC could be a further test to be included in the management of patients with filler complications.

We also found neck lymph nodes enlargement in 17 out of 26 patients (65%). Lymph node involvement concerned IA, IB, IIA and IIB cervical levels, characteristically draining the treated facial areas (36). These lymph nodes showed always an oval shape (longitudinal and axial axis ratio superior to 2) with longitudinal diameter up to 10 mm and smooth surface thus confirming their reactive aspect considering the imaging features (27). Considering the imaging characteristics, the survey of different signal

intensity between the enlarged lymph node and injected subcutaneous filler suggest the absence of foreign body reaction. In this study, patients were not elected for surgical removal of enlarged lymph nodes because it was not necessary for clinical purposes nor allowed by the Local Ethical Committee authorization.

Cooperation between radiologists and plastic surgeons is necessary in order to obtain the best diagnostic results using MRI. The aim is to offer optimal and customized care to patients presenting complications after filler injection for cosmetic purposes. MRI distinguishes among dermal filler complication (migration, granulomatous reaction, fibrosis), providing valuable information for treatment plan. MR multiplanar acquisitions defining precise anatomical landmarks offer the best imaging modality to evaluate filler migration; the i.v. administration of paramagnetic contrast media allows the differential diagnosis between inflammatory granulomatous reaction and subcutaneous fibrosis which doesn't show any significant contrast enhancement. Based on the diagnostic imaging results, when dislocation occurs surgery is planned; in case of granuloma medical therapy is our first choice and, if no improvement occurs, surgical removal is the next treatment option; in case of fibrosis lipofilling procedure and/or surgical removal are indicated.

In conclusion, regardless of its high cost, contrast-enhanced MRI should be recommended as a diagnostic tool in patients with severe late side effects after the injection of temporary and permanent facial dermal fillers, particularly when an inflammatory granulomatous reaction is suspected.

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Chapter 6

Radiolabelled white blood cells in the work out of dermal filler complications

Francesca R. Grippaudo[1], Marta Pacilio[2], Marco Di Girolamo[3], Rudi A. Dierckx[4], Alberto Signore[2,4]

[1]Plastic Surgery, [2]Nuclear Medicine and [3]Radiology Units, Faculty of Medicine and Psychology, "Sapienza" University of Rome, Italy.

[4]Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, The Netherlands.

European Journal of Nuclear Medicine & Molecular Imaging 2013;40:418-425

Key words: Dermal filler, scintigraphy, WBC, infection

Abstract

Purpose Scintigraphy with radiolabelled autologous white blood cells (WBC) is a widely used method for the detection of sites of infection. In this study we evaluated the role of WBC scintigraphy in the diagnosis and follow-up of patients with suspected soft tissue infection caused by dermal fillers in the face. We compared several qualitative and quantitative interpretation criteria and the results obtained
with MRI and high-frequency US (HFUS). ***Methods*** Between 2007 and 2011, ten consecutive patients (all women) aged between 25 and 65 years showing a reaction
to dermal fillers were enrolled in the study. In five of these patients WBC scintigraphy was repeated at the end of therapy. Scintigraphy with 99mTc-HMPAO-labelled WBC was performed in each patient acquiring planar and SPECT images at 3 h and 20 h as well as HFUS with Doppler analysis and MRI with Gd-DTPA. The final diagnosis was determined by fine-needle aspiration and microbiological analysis of lesions in eight patients (before therapy in six and after therapy in two) and by clinical data and follow-up (at least 1 year) in seven patients (before therapy in four and after therapy in three). Two patients were treated with steroids, and the others were treated with antibiotics for 3 weeks. Several qualitative and semi-quantitative interpretation criteria were applied to define the best strategy for accurate diagnosis of infections, implemented by SPECT images in patients with doubtful planar scans. The WBC scintigraphy results were also compared with the MRI and HFUS results. ***Results*** Sensitivity, specificity and accuracy were respectively 90 %, 100 % and 93.3 % for WBC scintigraphy with qualitative and semi-quantitative interpretation of planar images and 100 %, 100 % and 100 % with qualitative analysis of SPECT images. Sensitivity, specificity and accuracy for HFUS were 44 %, 66 % and 50 %, and for MRI

were 50 %, 100 % and 67.6 %, respectively. Scans performed after therapy in five patients were negative in three and still positive in two (all true results). ***Conclusion*** In conclusion, scintigraphy with radiolabelled WBC was found to be the most accurate method for diagnosing infection in patients with long-term dermal filler complications, particularly using qualitative analysis of SPECT images. No differences were observed with planar images using either qualitative or semi-quantitative analysis. HFUS and MRI may provide additional important information for defining the nature of the filler and for surgery, but are not accurate enough for diagnosing infection.

Introduction

Cosmetic tissue augmentation and correction of skin depressions using injectable material is not a new concept. In recent decades many new materials have been introduced into the market claiming to be permanent, inert, non-allergenic, well- tolerated, nonmigrating and easily removable if complications occur [1]. These materials can be divided in two classes according to the time they are present in tissues: temporary fillers and permanent fillers. The former are made with collagen
or hyaluronic acid and reabsorbed within a few months, whereas the latter are made of different materials (acrylates, polyalkylimide, liquid silicone) that stay at the site in the soft tissues for years [2]. These permanent substances are designed to be encapsulated by the body's own connective tissue and remain for a prolonged period or permanently to fill soft tissue deficiencies or for cosmetic amelioration.

Despite the minimally invasive nature of dermal fillers, there are some complications related to them [3]. Most common short-term complications, that appear within a few days of treatment, are bleeding, bruising or redness at the injection site and local oedema; these usually resolve spontaneously in a few days [4]. Long-term complications of

permanent fillers, whose onset is delayed months or years after treatment, are the formation of foreign body granulomas and abscesses, whose clinical signs are the formation of lumps in the soft tissue, often at sites distant from the area originally injected [5]. The aetiology of this lump formation is still debated, with some authors claiming that the lumps are due to an autoimmune response to the filler and others recognizing an infective process within the implants [6].

Since therapy is different (steroids or surgery for autoimmune forms and antibiotics before surgery for infected lumps) accurate pretherapy diagnosis of the nature of the

complication is mandatory [7].Scintigraphy with 99mTc-labelled white blood cells (WBC) is a procedure that has been proved to be reliable in detecting infections in hard and soft tissues [8–11]. In particular, there are well-established procedures for image interpretation of vascular graft infections, osteomyelitis and prosthetic joint infections. In the case of soft tissue infections and dermal fillers, in particular, the literature is very poor [12] with no clear image interpretation criteria. The aim of this study was therefore to apply several qualitative and semiquantitative interpretation criteria for suspected soft tissue infections from injected dermal fillers, in order to define the best strategy for accurate diagnosis of infections. In addition, we compared the results of WBC scintigraphy with those of MRI and high frequency US (HFUS) for the same purpose.

Material and methods

Patients

Ten consecutive patients with long-term reactions to dermal fillers were enrolled in the study between 2007 and 2011 (Fig. 1).

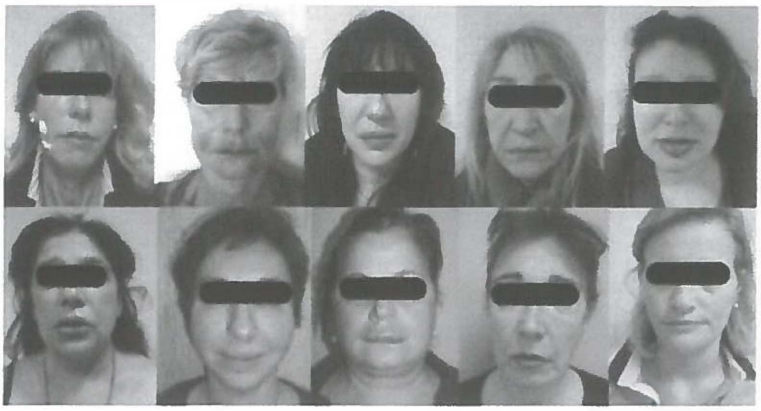

Fig. 1 Patients enrolled in the study after dermal filler injection for cosmetic purposes, showing filler-related complications in the soft tissues of the face

All patients signed an informed consent form, and approval was obtained from the local ethics committee. All patients showed lumps on the face at the nasolabial folds, zygomas or jowls, and one patient showed diffused indurations of both cheeks. All of the patients had had several episodes of redness and swelling of the face, previously treated with steroids. Four of the patients had received triamcinolone injected into the lumps, with transient effects.

At the time of scintigraphy all patients were afebrile and without any other clinical sign of an acute inflammatory process. The fillers were injected months to 8 years before the examination by plastic surgeons from other institutions, and consisted of liquid silicone, acrylates, hyaluronic acid and polyalkylimide, as also confirmed by US imaging according to published criteria [13, 14].

WBC scintigraphy Scintigraphy with 99mTc-HMPAO-labelled WBC was performed

in each patient as well as HFUS and MRI with Gd-DTPA as contrast agent.WBC scintigraphy was repeated after therapy in five patients. A standard protocol was used to label purified autologous WBC with 99mTc-HMPAO [15]. The whole procedure was performed in a laminar flow hood to prevent contamination. Planar gamma-camera images of the head were

acquired at 30 min, 3 h and 20 h after injection, and SPECT images were acquired at 3 h and 20 h. A gamma camera with a large field-of-view and a low-energy high resolution collimator was used (140 keV using a 15–20 % window). For planar images, time-corrected images for isotope decay were acquired at each time-point (i.e. 100 s at 30 min, 140 s at 3 h and 1,007 s at 20 h). This method, in which all images are represented with the same intensity scale, reduces operator interference in the final image interpretation and allows easier identification of increases in activity or size with time at infected sites. SPECT images were acquired at 3 h with a 30 s per step protocol with a matrix of 128-128 and with a 50 s per step protocol at 20 h.

Image interpretation Images were qualitatively assessed as follows: (a) negative, if no uptake or a significant decrease in uptake from 3 h to 20 h images was present, (b) positive, when uptake increased with time in late images with respect to early images, and (c) equivocal, when the uptake in early and delayed images was similar. After visual assessment, a semi-quantitative evaluation was also performed to determine whether quantification of uptake could help differentiate infection from sterile inflammation or granuloma. For this purpose, regions of interest were drawn over the region of the filler implant (target) and over the sagittal sinus (background). The mean counts per pixel in these regions of interest were recorded to calculate target-to-background (T/B) ratios both in early and delayed images (T/B_{early} and T/B_{late}, respectively). If the T/B ratio increased with time ($T/B_{late} > T/B_{early}$) by more than 10 %, the scan was considered indicative of infection; if T/B_{late} was similar to or slightly decreased with respect to T/B_{early}, the scan was classified as equivocal; if T/B_{late} was significantly decreased compared to T/B_{early}, the scan was classified as negative for infection. Reconstructed transaxial, sagittal and coronal images after SPECT acquisition were analyzed qualitatively as described for planar images. Infection was considered present if abnormal uptake was detected in the filler area.

Other examinations and follow-up HFUS was performed with Doppler analysis

Table 1 Imaging results in patients before and after antibiotic therapy

Patient no.	Patient ID	Before/after antibiotic therapy	Planar analysis			SPECT qualitative analysis[c]	MRI[d]		HFUS[e]	Final diagnosis
			Qualitative[a]	Semiquantitative[b]			Contrast enhancement	Adenopathy		
				T/B ratio 3 h	T/B ratio 20 h					
1	RF	Before	−	1.3	1.8	+	+	+	−	Infected. Swab positive. Antibiotic therapy
2	LL	Before	+	2.1	2.8	+	+	+	−	Infected. Swab positive. Antibiotic therapy then surgery
3	MGC	Before	+	2.4	2.7	+		+	+	Clinically judged infected. Antibiotic therapy
		After	−	2.4	2.1	−				Follow-up scan negative at 2 months. Still in clinical remission after 3 years
4	BD	Before	++	1.8	2.3	+	+	−	+	Clinically judged infected. Antibiotic therapy
		After	+	1.4	1.7	+				Follow-up scan positive at 3 months. Repeated antibiotic therapy course. Clinical remission at 18 months
5	ER	Before	−	2.3	2.1	−		−	−	Judged noninfected after all tests. Steroid therapy. Still in clinical remission after 3 years
6	CP	Before	+	1.0	1.4	+	+	++	−	Infected. Swab positive. Antibiotic therapy
		After	+	1.2	1.6	+	+	+	+	Control scan positive at 2 months confirmed by a positive swab. Repeated antibiotic therapy course but still infected 6 months after the second course
7	CDP	Before	+	2.1	2.1	+		−	−	Clinically judged infected. Antibiotic therapy
		After	−	1.5	1.2	−				Follow-up scan negative at 3 months. Still in clinical remission after 4 years
8	MS	Before	+	1.9	2.6	+			+	Infected. Swab positive. Antibiotic therapy
9	MR	Before	+	2.3	2.8	++		+	−	Infected. Swab positive. Antibiotic therapy
		After	−	1.6	1.2	−		−	−	Follow-up scan negative at 6 months. Filler removed surgically and negative histology for leucocytes
10	GD	Before	−	1.5	1.3	−	−	−	+	No infection. Swab negative. Steroid therapy

[a] Infection criteria: increase of uptake with time from early to delayed images.

[b] Infection criteria: increase in T/B ratio with time ($T/B_{late} > T/B_{early}$) of more than 10 %.

[c] Infection criteria: abnormal uptake in the filler area.

[d] Infection criteria: contrast enhancement and/or adenopathy.

[e] Infection criteria: presence of fluid collection around filler with adenopathy

using a Hitachi H21 apparatus (Hitachi Medical Corporation, Tokyo, Japan) equipped with a high-resolution probe (10–13 MHz for small parts). MRI was performed with a 1.5-T superconductive unit (Sonata; Siemens, Erlangen, Germany) using a head and neck coil. Six patients received intravenous administration of Gd-DOTA (Dotarem, Guerbet, France), at a dose of 0.1 mmol/kg. The MR acquisition was started 2– 3 min after injection of contrast medium. T1, T2 and fat saturation
images were acquired. Swabs In six patients (before therapy in five and after therapy in one) whose results were suggestive of infection and two patients (before in one and after therapy in one) with no signs of infection a culture swab was obtained from the affected area, with microbiological culture or histological examination of surgical material. Ceftriaxone (Rocefin) 1 g intramuscularly for 7 days combined with ciprofloxacin (Ciproxin) 500 mg twice daily for 3 weeks was prescribed by the Infectivologist for all patients with positive and doubtful results. All patients returned for scheduled follow-up at intervals of 6 months. In some patients the follow-up was extended to 2 years, and in others to 5 years.

Results

Being a retrospective study, scintigraphy, MRI and US were reported by the physicians before knowing the results of microbiology, and therefore should be considered as blind readings. Scintigraphic examinations were well tolerated by the patients and no adverse reactions occurred. WBC scintigraphy was performed before therapy in ten patients and after therapy in five patients (total 15 scans; Table 1 and Figs. 2 and 3).

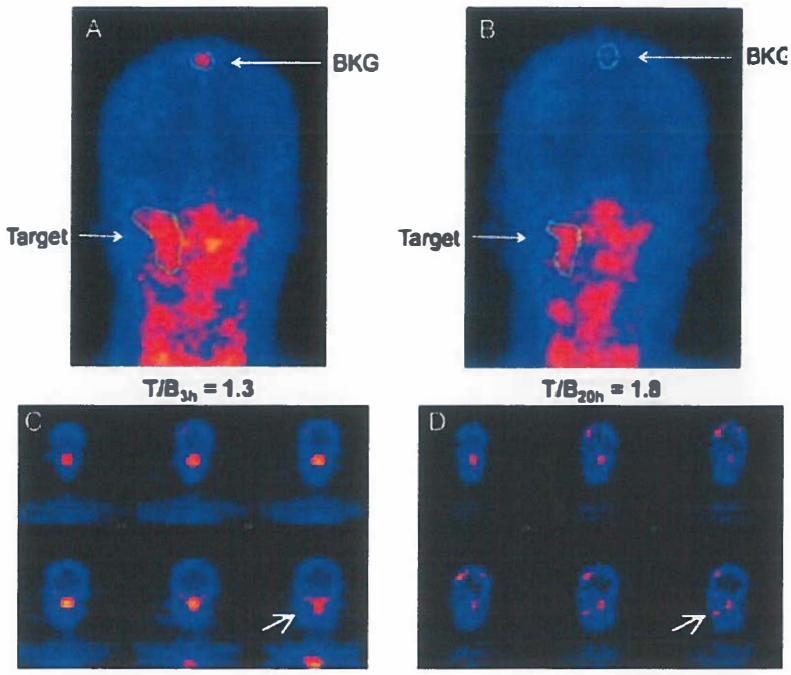

Fig. 2 Anteroposterior scintigraphic images in patient 1 (RF). a, b Planar images do not clearly show an increase in uptake between 3 h (a) and 20 h (b). The scan was judged negative by qualitative analysis but semiquantitative analysis showed an increase in T/B ratio (from 1.3 to 1.8) in the right zygomatic region (*Target*) (*BKG* background). c, d Coronal SPECT images. The positive area is more clearly visible at 3 h (c) and at 20 h (d) (*arrows*)

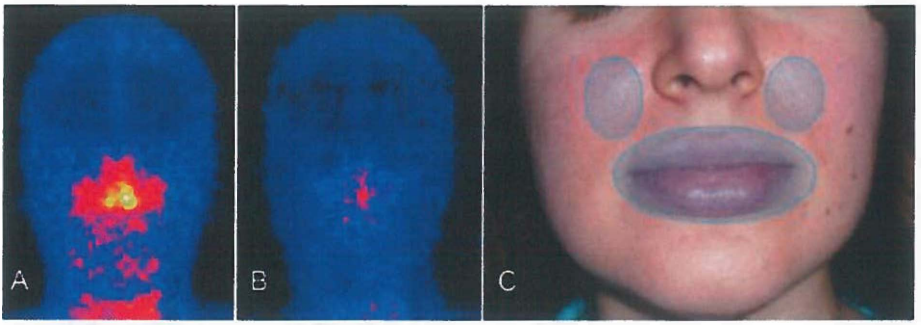

Fig. 3 Anterior planar images in patient 5 (ER). a, b The scan was judged negative by both qualitative and semiquantitative analysis (a T/B_{early} 2.3, b T/B_{late} 2.1). c Photograph of the patient at enrolment showing the areas of filler complications

Of these patients, ten had an infection and five did not. Qualitative interpretation of planar WBC scans showed positive results in nine patients and negative results in six (one false-negative). By semiquantitative analysis of the planar images, nine patients were judged to have infection, one was equivocal and five were negative (one false-negative). By SPECT, ten patients were positive and five were negative (all true positive results) (Fig. 4). The patient-based analysis showed sensitivity, specificity and accuracy of 90 %, 100 % and 93.3 %, respectively, for the qualitative and semiquantitative interpretations. The culture swabs taken from the areas previously injected with the dermal filler confirmed the results of the scintigraphic examination.

Infection was confirmed or excluded by microbiology in eight patients. In two patients, after the antibiotic course surgical excision was planned and histology was obtained, showing the presence of granuloma. The combination of ceftriaxone and ciprofloxacin improved the symptoms in all patients. All patients remained free of clinical relapse after 12 months of follow-up, although two patients still showed signs of infection on the follow-up scintigraphy scan. In these patients the therapy course was repeated and one of the two did not show any infection after 2 years of follow-up. No side effects were seen in any patient.

HFUS showed a 44 % sensitivity, 66 % specificity and 50 % accuracy of 44 %, 66 % and 50 %, respectively, for the diagnosis of infection. However, HFUS was primarily performed for determining the presence and nature of the filler, for which it has a high accuracy [13, 14]. MRI showed well the presence of the filler and associated adenopathy that was considered a sign of infection, together with positive signal enhancement after Gd-DOTA administration. On this basis, the sensitivity, specificity and accuracy for showing the presence of infection were 50 %, 100 % and 67.6 %.

Discussion

Data from the American Society of Plastic Surgeons reveals that 1.2 million dermal filler procedures were performed in the US in 2008, and 1.7 million in 2009, with a growing trend [16]. Data on the incidence of complications have never been systematically collected and reported. Complications depend on the type of filler agent used and institution. Estimated rates range from 0.08 % for hyaluronic acid (not a permanent filler) to 10 % for acrylates and up to 50 % or more for poly(lactic acid) [17, 18].

Infections are reported as rare complications after dermal filler injections [19]. Comprehensive statistical data are also lacking in the medical literature. Infections are mainly reported as case reports, and have been investigated in a study of patients treated with a single filler at different percentages from 0.2 % to 19 % according to the type of filler [20]. In the last few years, however, growing attention has been focused on granulomatous reactions, whose frequency in the US has been reported to be between 0.1 and 0.001 % for all implants. Granulomas may hide infection [21]. The FDA has approved only five compounds as dermal fillers: hyaluronic acid, collagen, hydroxyapatite, poly(Llactic acid) and poly(methyl methacrylate) microspheres [22].

In Eastern countries and Europe, there are more than 100 different fillers on the market, and the incidence of granulomas and granuloma-related infections is much higher than in the US and is rapidly increasing. In our institution, we see patients with dermal filler complications referred to us from all over Italy. From 2007 to 2011, 200 patients were referred. The majority of complications were cosmetic due to filler dislocation or overtreatment. Ten patients with acute infection with evident pus discharge from cutaneous fistulae were not included in the study.

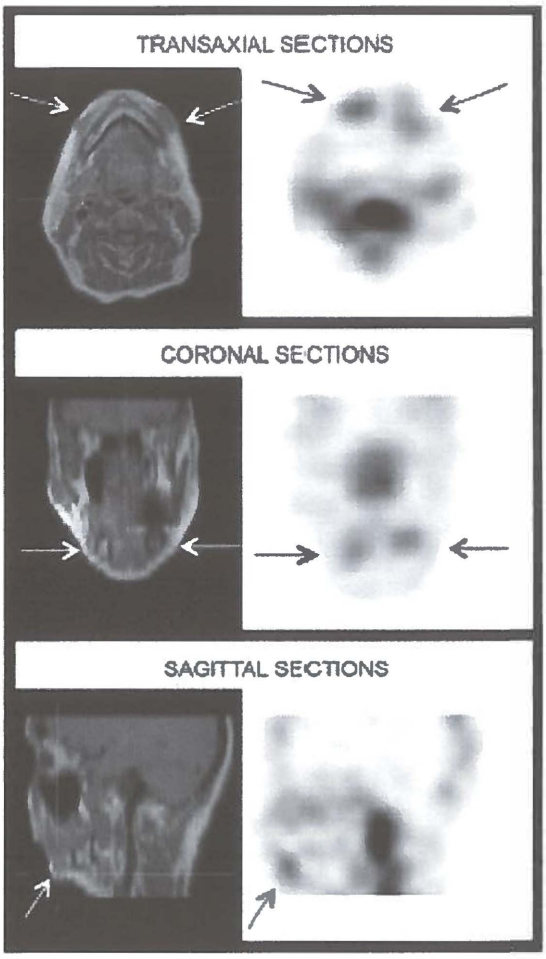

Fig. 4 Transaxial, coronal and sagittal MRI (fat-suppressed) and SPECT images in patient 9 (MR) 3 h after WBC injection. The filler is easily detectable in the MRI images and shows positivity in the WBC scintigraphy images (*arrows*)

Only patients with clinical suspicion of low-grade infection (ten patients) were included in this study and eight of these had an infection. Therefore, we observed an overall incidence of infection of 18 out of 200 patients (9 %). A granulomatous process due to foreign body reactions or chronic infections

may appear in a time period ranging from months to years after injection of various dermal fillers. Sanchis-Bielsa et al. [23] hypothesized that the appearance of a granuloma represents a delayed hypersensitivity phenomenon caused by unknown factors, similar to orofacial granulomatosis.

Christensen has shown that, if treated with steroids, infections from polyacrylamide hydrogels due to contamination at the time of treatment or latermight progress to a biofilm community of bacteria leading to a chronic low-grade infection, resistant to usual antibiotics doses [18]. Bacterial infections contaminating dermal fillers cannot be easily detected with routine bacterial swabs. Fluorescence in situ hybridization using peptide nucleic acid probes on samples obtained from biopsy and observed by epifluorescence microscopy has been shown to be able to detect bacterial contamination in samples negative on haematoxylin and eosin (H&E) staining [24]. In our study, scintigraphy with radiolabelled WBC helped determine the nature of the inflammatory process, and showed the presence of a previously undetected chronic inflammatory process or an active infection in all patients with very high accuracy. Some authors have advocated the use of local steroid injections or intradermal 5-fluorouracil to treat the adverse effects of permanent filler [4], but these treatments can cause secondary lesions ending with skin atrophy or discoloration. Treatment such lesion with steroids might lead to severe panniculitis, recurrent oedema, fistula formation and subsequent tissue scarring [7]. The qualitative analysis of planar WBC scintigraphy images was false-negative in one patient, as was the semiquantitative analysis of planar images (although a different patient); these were both clarified by SPECT imaging despite the absence of hybrid imaging. Overall, the high accuracy of WBC scintigraphy was confirmed for soft tissue infections, as previously reported by others, using as a positive criterion an increase in uptake in late images compared to early images. In the studied patients the clinician suspected infection and therefore we had a high incidence of final infections that may have affected the calculation of the

sensitivity of the different imaging modalities. However, we focus on the complementary role of the different imaging modalities and on the high specificity ofWBC scintigraphy for detecting infection in this group of patients. Hovi [9] used only 3-h and 6-h images for investigation of soft tissue infections and qualitative criteria and found a specificity of 100%, but he studied only patients with peripheral osteomuscular infections. Concerning facial soft tissue infection, there is a case report by Sayit et al. [10] who used 4- h and 24-h images and a qualitative approach. We also agree with these acquisition time points for facial infections due to the high vascular background of this anatomical area. In an interesting study in vascular graft infections, Vorne et al. [25] acquired images at 2 h, 6 h and 24 h and found that 24 h images provide a better target to background ratio than images at 6 h (except for grafts located in the abdomen due to bowel extretion of free 99mTc-HMPAO). In our study, in a large series of patients with infection considered to be associated with dermal filler, we compared qualitative analysis with quantitative analysis using T/B ratios and SPECT images. The quantitative analysis was a more objective tool for image interpretation with a diagnostic accuracy of 93.3 % (only one patient was considered false negative in the qualitative analysis, but had an equivocal result with T/Bearly equal to T/Blate). The SPECT images helped clarify doubtful planar images, but in this study analysis of SPECT images was not relevant if quantitative analysis of planar images was performed. We chose the sagittal sinus as the background area for quantitative analysis so as to eliminate the vascular contribution in the target area. HFUS is an operator-dependent investigation that does not allow a second opinion in the evaluation of the diagnostic images. It can identify granuloma as lumps with irregular sonographic patterns without a distinctive border from soft tissue, and abscesses as fluid collections around the implant, as well as the presence of enlarged lymph nodes. Patients with a history of chronic inflammation often show a hyperechoic wall around the implant, but it is not always possible to distinguish between a fibrotic reaction and an infection.

Although in this study HFUS and MRI showed a low diagnostic accuracy in detecting infection of the soft tissue after dermal filler treatment, HFUS showed the nature, size and position of the filler and the presence of granuloma or abscesses, and MRI better showed the size and spatial position of the filler with respect to anatomical landmarks, and was useful for planning surgical removal. It also shows the presence of granulomas and fibrotic reaction but cannot discriminate between septic and aseptic inflammation, which is what nuclear medicine provides.

In this context the complete characterization of these patients before surgery necessarily should include all three examinations that provide different and complementary data. In conclusion, scintigraphy with radiolabelled WBC was shown to be the most accurate imaging method for the diagnosis of infection in patients with long-term dermal filler complications. For high diagnostic accuracy, images should be acquired with correction for isotope decay halflife and interpretation should be qualitative (accuracy 93.3 %) and semiquantitative (accuracy 93.3 %) on planar images, with interpretation on SPECT images (accuracy 100 %) implemented in patients with doubtful planar scans. Laterolateral acquisitions were not more helpful than the anteroposterior planar acquisitions and the SPECT images.

Since accuracy of the SPECT only was very high, hybrid SPECT/CT imaging may not be necessary. If, however, SPECT/CT can be performed, the CT could replace the MRI. Nevertheless the combination of SPECT and MRI is associated with less radiation exposure than SPECT/CT.

MRI and US both have low accuracy (67.6 % and 50 %, respectively) for diagnosing infection, but HFUS should routinely be performed to confirm the presence and nature of the dermal filler, since treatment differs for different materials. MRI is indicated for the precise anatomical localization of the filler and to diagnose a fibrotic reaction, information that is useful to the plastic surgeon, and avoids further radiation exposure as compared to CT.

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Chapter 7

Conclusions and future perspectives

In the previous sections of this Thesis it was highlighted the complications after dermal filler injections for cosmetic augmentation, the potential of the imaging resource in their diagnosis analyzing the limits and the different characteristic of HFUS, MRI and Scintigraphy (1-3).

All these techniques have a distinct and peculiar role in the diagnostic process: HFUS identify the presence, quantity, type and site of the foreign material, MRI identify the presence, quantity and site of the filler showing its relationship with the anatomical landmarks, scintigraphy detects the presence of infections and monitors the efficacy therapy (table 1).

As indicated in the chapters, all these techniques have direct implications in therapy planning, that could request a medical or surgical or a combined approach, and can be of help in excluding soft tissues neoplasms (4).

Each year new dermal fillers received the CE marks and are introduced in the market.

According to statistics of the American Society for Aesthetic Plastic Surgery, cosmetic enhancement of the soft tissue achieved through dermal filler injection, is the second non surgical procedure for number of patients treated each year.

With the widespread use of dermal filler injections, subsequent infection/ inflammation or granuloma have increased, thus the necessity to apply different imaging techniques to complement the clinical exam and the anamnesis.

In the future it would be important to identify any different filler implanted for cosmetic reason and, with a perspective study, obtain an imaging study of the interactions between these products and the human tissues.

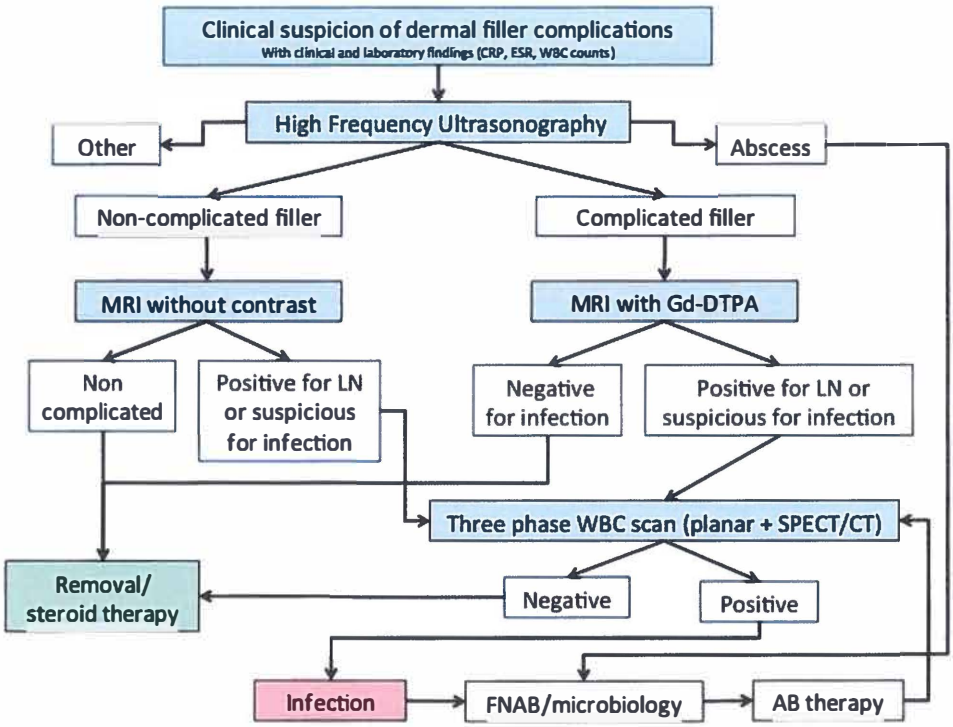

Table 1

Diagnostic flow-chart in dermal fillers

We still don't know the fate of most foreign materials, when injected as dermal fillers in soft tissues of the face or in other body's areas. Very few long term studies (>3 years) are present in the medical literature (5, 6) and on few dermal fillers only. It is advisable to study the fate of these materials to detect the long term interactions with tissues.

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Chapter 8

Summary

The main topic of the present Thesis is the diagnostic role of imaging when dealing with dermal fillers complications. Dermal fillers injections may cause short and long term complications, with infective, fibrotic, granulomatous process that require different therapeutic approaches.

My original contribution to knowledge is to have developed a method to approach the above mentioned complications, and in order to look for the best treatment to remove these foreign materials after their migration, even when they diffusely infiltrated the soft tissue of the face, without any cleavage plane. Then it became clear that to treat dermal filler complications it was of paramount importance to know what filler was involved, where it was, and to distinguish between inflammations and infections, these last often sub-chronic.

Imaging plays a major role to help the physician in the diagnostic pathways, and several techniques were investigated to understand each peculiar role.

Several different aspects related both to surgery and to safety of the patients were discussed. In particular, in chapter 2, regional ultrasound and MRI were useful to diagnose the presence of siliconomas, when evaluating three patients with lumps in the face or in the breasts and with anamnesis of filler injections. After imaging the procedure was completed, and the nature and extension of the lumps within the soft tissues ascertained. Ultrasonic liposuction procedure was then used to remove siliconomas. Before this study, the traditional methods of removing siliconomas have been excision of the affected tissues or suction of the injected silicone. Unfortunately

siliconomas are often found in exposed areas, where it is undesirable to leave visible scars, and suction is technically difficult and often unsuccessful because the affected tissues are hard. Postoperative MRI consented to ascertain the reduction of the liquid silicone injected in the soft tissues due to ultrasonic liposuction. This surgical approach results in clinical improvement in all patients, after a mean follow up of 38 months (range 18 months-4 years).The only problem was a minor burn at the entrance port in one patient.

Because of the plethora of existing filler, who differ in composition and biological behaviour, and because patients presenting complications after dermal filler treatment often ignore which material has been implanted in the soft tissues, nor have any leaflet product or have lost contact with the physician that originally injected the product, it is important to first evaluate what and where the dermal filler is placed in the soft tissues.

In chapter 3 the role of High Frequency Ultrasound (HFUS) to evaluate dermal fillers and their complication was originally investigated in two groups of patients, all having received a known injection of dermal filler in the soft tissue of the face. The sample was composed of 36 patients, divided in two groups. Group A included 20 patients after temporary fillers (Hyaluronic acid or collagen), and group B included 16 patients after injection of permanent dermal fillers (Aquamid, Bio Alcamid, Matridex and Liquid silicone). The study groups underwent a US scan by a physician blinded to the filler injected. All the patients had their upper lip or nasolabial fold scanned using high-frequency US, according to the site of filler augmentation. The exam was performed with a Hitachi H21(Hitachi Medical Corporation, Tokyo, Japan), with a high-resolution probe 10–13MHz for small parts. HFUS proved to be a reliable technique in detecting the presence of these dermal fillers in the soft tissues of the face, the size of the filler was measurable, and the exam was well tolerated by the patients. This study highlighted a different sonographic pattern among temporary and permanent fillers and silicon infiltrated in the soft tissues.

After the validation of HFUS to detect the presence of different filler within the soft tissue of the face, the next step was to study the visualization limits of this technique and give the estimate costs of this procedure. In Chapter 4 the use of HFUS in dermal fillers diagnosis was further investigated to ascertain the site, quantity, and type of filler injected in the soft tissue of the face, with respect to reliability of the procedure and the analysis costs.

A sample of 80 patients having received filler injection in the soft tissues of the face for cosmetic purposes were submitted to HFUS with a high resolution probe for small parts (10-13 MHz). In this study were enrolled healthy patients – Group A (42 pts) and patients showing local complications – Group B (38 pts), consisting in product palpability, filler migration, lumps, acute and chronic infections, and pain. Often, multiple complications presented in the same patient.

In both groups were included patients after injection of temporary dermal fillers (hyaluronic acid, collagen), permanent dermal fillers (Matridex, Aquamid, Bio Alcamid, liquid silicon, Goretex threads, hydroxyapatite).

The examination was performed with a Hitachi H21 (Hitachi Medical Corporation, Tokyo, Japan), with a high-resolution probe 10 to 13 MHz small parts. Ultrasound gel (Aquasonic gel 100, Parker Laboratory, Fairfield, NJ) was applied on the site to explore, and often a silicon gel pad (Aquaflex, Parker Laboratory, Fairfield, NJ) was interposed between the probe and the skin to overcome the lack of resolution in the first 2 to 3 mm. and to obtain a better image on uneven surfaces.

The results showed that it was possible to detect and measure the filler in the vast majority of the sample (97.5% of cases), with the minimum size identifiable was of 1 mm, even when its presence was not detected at clinical evaluation.

It was possible to detect inflammatory reaction, granulomas, and recognize the presence of diverse fillers in the same area.

Dermal fillers showed different sonographyc patterns. Liquid silicone injected in the soft tissue has a typical appearance as "snowstorm" due to a strong acoustic shadowing of scattered and reverberating echoes with well-defined anterior margin and a posterior loss of details. Temporary fillers appears as hypoechoic mass without internal echoes; Matridex appear as hypoechoic mass with internal echoes; acrilates (Aquamid and Bio Alcamid) as hyperechoic lumps. The examination was well tolerated by all patients, lasting a mean of 20 minutes.

After this study, the role of HFUS in dermal fillers investigation as an aid in detecting the presence and seldom the nature of the filler implanted in the soft tissue of the face was ascertained. To be able to recognize the presence of a dermal filler, even if not evident at clinical exam, is of paramount importance when considering that interactions among diverse fillers are still under investigation, and manufacturer's guidelines warn against the use of different materials in the same site, because of the risk of complications.

HFUS consented to detect the presence of an implant and, often, its identification even in the absence of medical documentation: knowing what material is already implanted before attempting further treatments can dramatically reduce complication rates and unfavorable results.

In clinical practice long term complications after dermal filler injections presents as diffuse recurrent oedema of the soft tissues, and/or lumps, and/or fistulae formation with or without discharge, and/or chronic or recurrent pain and/or fever.

In order to offer the best treatment plan to patients presenting with complications it is of paramount importance to make a distinction among infective processes and inflammatory reactions. The aetiology of this lumps formation is still debated, with some Authors claiming to be due to an autoimmune response to the filler and others that recognise an infective process within the implants. Despite the suspected nature of an infective process, most of the swabs that are taken during surgical removal fail to detect

a pathologic agent. HFUS does not give to the plastic surgeon a visualization of the material with respect to the anatomical structures, an useful aid when planning surgery.

In chapter 5 the role of MRI was investigated to ascertain its usefulness to detect the presence of filler injected in facial soft tissue and characterize complications with contrast-enhancement. A first series of 19 patients treated with dermal filler for cosmetic purposes in the face (10 after temporary and 9 after permanent filler) were submitted to MRI to ascertain if MRI could visualize the injected product. TSE-T1-weighted, TSE-T2-weighted, fat-saturated TSE-T2-weighted and TIRM scans on axial and coronal plane were performed. It was always possible to detect and measure the foreign materials. Temporary dermal fillers appeared as hypointense spots in T1-weighted and hyperintense in T2-weighted images. Permanent fillers appeared as hypointense spots in T1-weighted images while the signal intensity in T2-weighted images varied.

Following the results of first group 26 more patients with filler-related complications, clinically diagnosed (pain, inflammation, ulcers, edema, redness, lumps) were enrolled to evaluate if contrast-enhanced MRI was able to characterize the lesion. After the TSE-T1-weighted, TSE-T2-weighted, fat-saturated TSE-T2-weighted and TIRM scans on axial and coronal plane, fat-suppressed TSE-T1-weighted scans were performed after i.v. administration of Gadolinium-DOTA. In patients with complications, T2-weighted images showed granuloumatous reactions confirmed at biopsy. In complicated cases, cervical lymph node enlargement was also detected.

After this study it is possible to propose the role of MRI in dermal filler imaging as s a useful and non-invasive tool for anatomical localization of facial dermal filler. If complication occur, i.v. Gadolinium administration is advised for better characterization of the lesion. MRI consented the dermal filler visualization with respect to the anatomical structures of the face, thus easing the problem comprehension for the patient and easing the surgical planning in case of removal.

In chapter 7 the innovation element was to apply scintigraphy with ^{99m}Tc-labelled white blood cells, a procedure that has proved to be reliable in detecting chronic infections in hard and soft tissues, to evaluate the nature of the lumps in patients with complication.

In this study ten patients, aged 25 and 65 years, presenting lumps after cosmetic treatment of the face, were enrolled and evaluated with 99mTc-WBC scintigraphy. Four of them referred an history of local triamcinolone injections in the lumps with a transient effect only.

HFUS and RMI were done to detected the presence of the fillers in each patient, consisting in liquid silicone, acrilates, hyaluronic acid and polyalkilimmide. Then ^{99m}Tc-HMPAO labelled leukocytes scintigraphy was performed in each patient. Leukocytes were isolated by sedimentation of 50 ml of blood (using acid citric dextrose as anticoagulant agent) added with 10% Hydroxy-ethil starch, followed by centrifugation and labelling with ^{99m}Tc-HMPAO (20-25 mCi), and injected intravenously (i.v.) into the patient (10-15 mCi). Planar and SPECT gamma-camera images of the head were acquired after 30min, 3 h and 20 h. Several qualitative and semi-quantitative interpretation criteria to suspected soft tissue infections to define the best strategy for accurate diagnosis of infections, implemented by SPECT images in case of doubtful planar scans.

The images were classified as (a) negative if no uptake or a significant decrease in uptake from early to delayed images is present, (b) positive when uptake is seen in both early and delayed images which increases in time, and (c) equivocal when the uptake in early and delayed images is the same or slightly decreasing.

Four pts whose result was suggestive for infection, as well as one patient with clinical signs of infections but with a negative result, underwent cultural swabs from the suspicious area. Swabs confirmed the infective process. An association of Ceftriaxone 1g im (Rocefin®) for 7 days and Ciprofloxacin 500mg (ciproxin®) tablet /2d for three weeks was prescribed by the Infectivologist to all

positive and doubtful pts. After the therapy five pts repeated the scintigraphy, according with the described protocol.

In conclusion, the scintigraphy with radiolabelled WBC showed to be the most accurate method to diagnose infection in patients with long term dermal filler complications. For high diagnostic accuracy, images should be acquired with time corrected for isotope decay and interpretation should be qualitative and semi-quantitative, implemented by SPECT images in case of doubtful planar scans. Latero-lateral acquisitions were of no help, respect to the antero-posterior planar acquisitions and the SPECT images. MRI and US have both low diagnostic accuracy for infection, but US should routinely be performed to confirm the nature of dermal filler, since treatment may differ for different materials. MRI is of help for the anatomical localization of the filling, particularly to identify those fillers that migrate from original injection site and, therefore, provide useful additional information to the plastic surgeon.

Chapter 9

CURRICULUM VITAE

Francesca Romana Grippaudo, MD

EDUCATION AND TRAINING

Francesca Romana Grippaudo was born in Roma, Italy, on 13 January 1961. Married, has one child, born in 2003.

She graduated Magna cum Laude in Medicine and Surgery in 1985 at the School of Medicine, La Sapienza University of Rome, Italy.

Undergraduate students she did one month elective stages in General Surgery in 1981 (Glostrup Hospital, Copenhagen,DK), in 1982 (Hadassah Medical Centre, Jerusalem, Israel); and Plastic Surgery in 1983 (Dijkzigt Hospital, Rotterdam, NL); in 1984 (Sabbatsberg Hospital, Stockholm, S).

From 1986 to 1991 she undertook the postgraduate training in Plastic Surgery at "La Sapienza" University of Roma, Italy, Program Director: Prof N Scuderi, and graduated Plastic Surgeon the 4 of November 2001, magna cum Laude.

APPOINTMENTS AND POSITIONS

1987-1988: Emergency Doctor for Red Cross Organisation in Rome, Italy.

12,1988-2003: Assistant Professor of Plastic Surgery, Plastic Surgery Division, Policlinico Umberto I, La Sapienza University of Rome, Italy.

01-08,1992: Honorary SHO, Plastic surgery Unit, Mount Vernon Hospital, Northwood, (Sabbatical) Middlesex, UK

01-08,2006: Plastic Surgeon Fellow, Plastic Surgery Unit, Mater Hospital, Brisbane, (Sabbatical) Queensland, Australia

2003-present: Assistant Professor of Plastic Surgery, Plastic Surgery Unit, S. Andrea Hospital, Faculty of Medicine and Psychology, Sapienza University of Rome, Italy.

2007-present: Vice President, Orthopaedic Technicians School, Faculty of Medicine and Psychology, Sapienza University of Rome, Italy.

MEMBERSHIP IN PROFESSIONAL AND SCIENTIFIC SOCIETIES

From 1987 Società Italiana di Chirurgia Plastica, Ricostruttiva ed Estetica

From 1992 International Confederation for Plastic and Reconstructive Surgery

From 1999 British Association of Plastic Surgeons

SCOLARSHIPS AND GRANTS

1986 National Centre for Research (C.N.R.) grant for research in Plastic Surgery, with a project on Rehabilitation for the oncologic patient. Part of the research was done in UK Plastic Surgery Units (Mount Vernon Hospital, Northwood; Saint Andrew Hospital, Billericay; Canniesburn Hospital, Glasgow; The Royal Marsden Hospital, London).

1989 Italian Health Ministry grant for research in Social Medicine Diseases.

HONORS

2002 European Federation of Orthodontics 2002. Best Scientific Paper published in 2001.

INTERNATIONAL VOLUNTEER SERVICE

2001 Interplast Italy, Dhaka, Bangladesh, Volunteer Surgeon

1996 Queensland Friend of Operation Smile, Olongapo, Philippine, Volunteer Surgeon

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Chapter 10

Acknowledgements

This thesis is the end of my journey in obtaining my PhD. I have not traveled in a vacuum in this journey. This thesis has been kept on track and been seen through to completion with the support and encouragement of numerous people including my well wishers, my friends, colleagues and various institutions. At the end of my thesis I would like to thank all those people who made this thesis possible and unforgettable experience for me. At the end of my thesis, it is a pleasant task to express my thanks to all those who contributed in many ways to the success of this study and made it an unforgettable experience for me.

First and foremost my sincerest gratitude to my supervisor Prof Dr Alberto Signore, who has supported me throughout my thesis with his patience and knowledge whilst allowing me the room to work in my own way. I attribute the level of my PhD degree to his encouragement and effort and without him this thesis would not have been completed or written. One simply could not wish for a better or friendlier supervisor.

Special thanks should also be given to Prof Dr Nicolò Scuderi, my other supervisor. Thank you for introducing me to the study of Plastic Surgery many years ago, for your continuous support and guidance in the years that followed and for keeping me motivated throughout the writing and editing of the articles bound in this thesis. Thank you for creating various opportunities for me, believing in me and giving me the necessary pep-talks whenever I started doubting myself. Your passion for the field of our common specialty is contagious. I hope that there will be many more collaborations between us in the time to come.

A special thank to Prof Rudy Dierckx, who provided an experienced ear for my doubts about writing a thesis, and moreover gave me the willingness and opportunity to follow my ideas and complete my researches in such a prestigious university as Groningen.

I want to thank all the students and doctors that have Listened to the Annual Reports of activities offering their useful positive criticism and raising new points of interest .

Thanks to Dr Mauro Mattei and Dr Marco Di Girolamo who have helped me with all the Ultrasound and MRI studies included in this thesis as well as many others, with consistent quality.

In my daily work I have been blessed with a friendly and cheerful group of colleagues: a heartfelt thank you to the following individuals: Marta Pacilio who helped me with to analyze the data after scintigraphic exam and Luca Renzi always ready to help with organization duties.

I am grateful for my sister Cristina and friend Adrienne Brower for being my paranimphs.

I am also indebted to the many librarians that have helped me during all these years in my bibliographic researches: thanks chaps, keep up the good work.

Finally, I thank my husband and my family for supporting me throughout my studies with their patience and loving cares.