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ORIGINAL ARTICLE

Radiolabelled white blood cell scintigraphy in the work-up of dermal filler complications

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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 ^{99m}Tc-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 semiquantitative 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 semiquantitative 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 semiquantitative 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.

Keywords Dermal filler · Scintigraphy · WBC · Infection

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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 ^{99m}Tc-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.

Materials and methods

Patients

Ten consecutive patients with long-term reactions to dermal fillers were enrolled in the study between 2007 and 2011 (Fig. 1). 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 ^{99m}Tc-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 ^{99m}Tc-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 semiquantitative 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

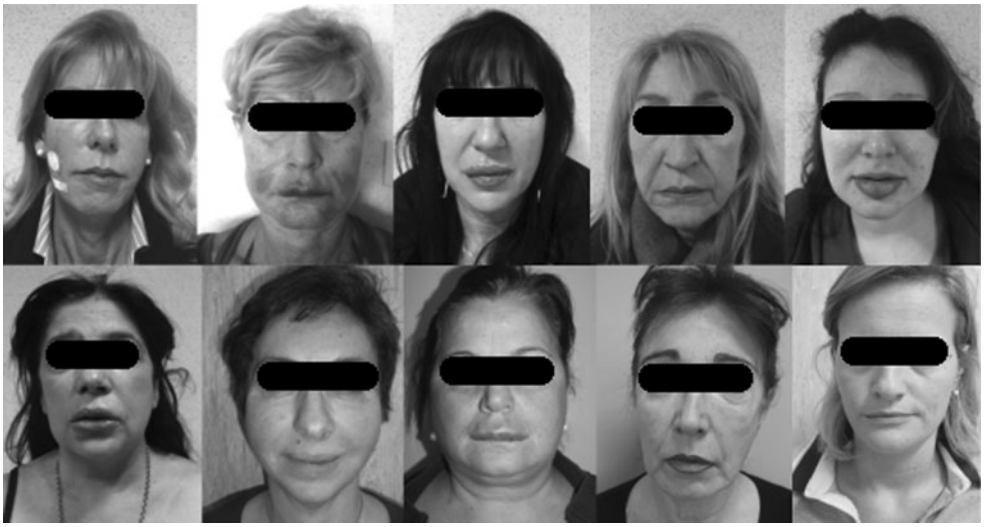

Fig. 1 Patients enrolled in the study after dermal filler injection for cosmetic purposes, showing filler-related complications in the soft tissues of the face

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 analysed 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 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 infectologist 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). 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

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

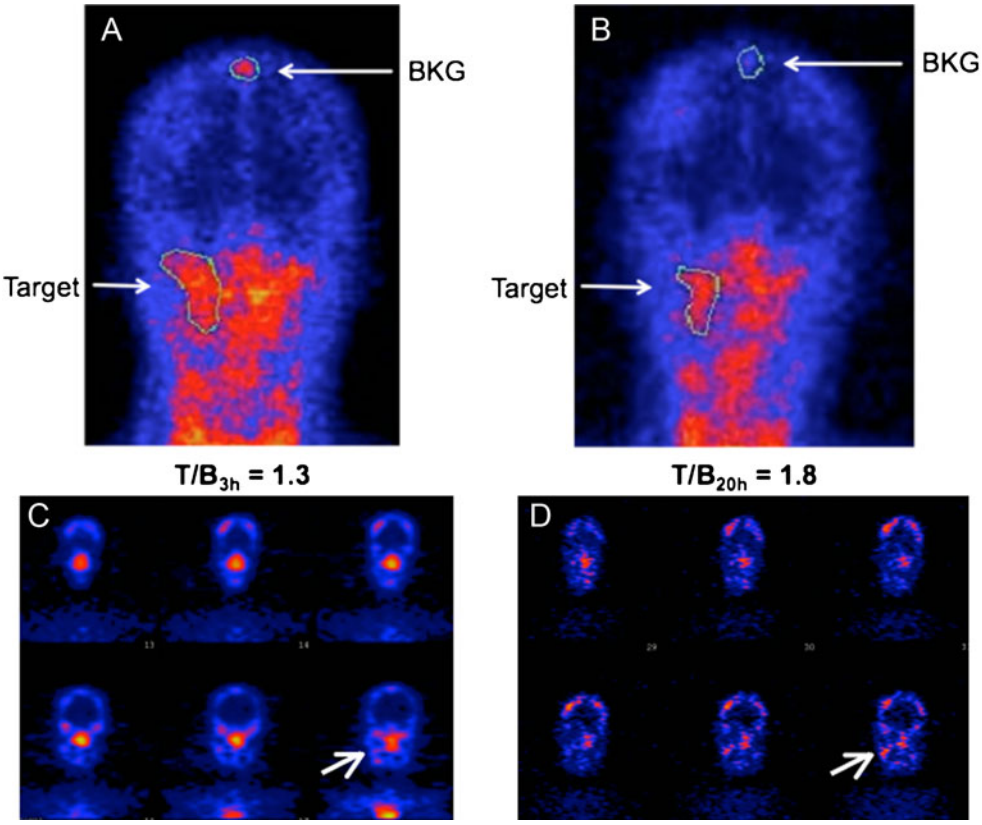

Fig. 2 Anteroposterior scintigraphic images in patient 1 (RF). **a**, **b** Planar images do not clearly show an increase in uptake between 3 h (**a**) and 20 h (**b**). The scan was judged negative by qualitative analysis but semiquantitative analysis showed an increase in T/B ratio (from 1.3 to 1.8) 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*)

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

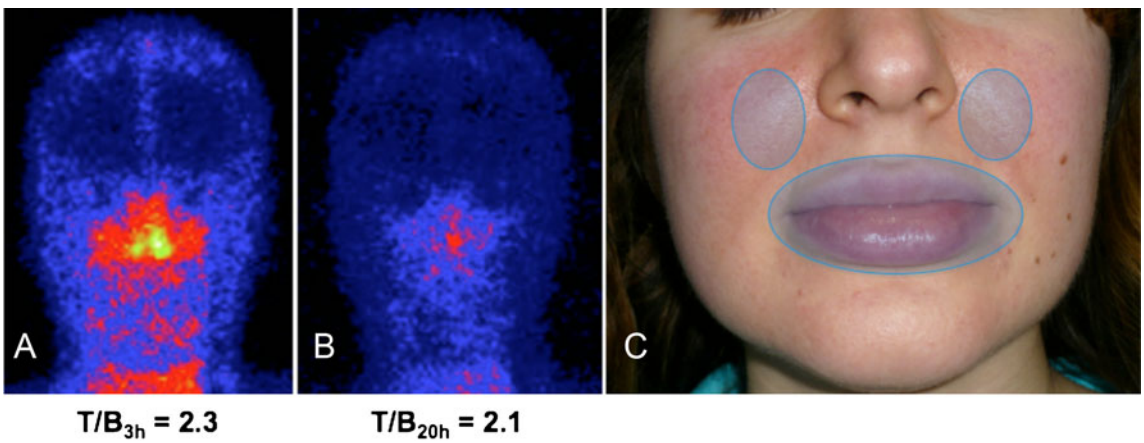

Fig. 3 Anterior planar images in patient 5 (ER). **a**, **b** The scan was judged negative by both qualitative and semiquantitative analysis (**a** T/B_{early} 2.3, **b** T/B_{late} 2.1). **c** Photograph of the patient at enrolment showing the areas of filler complications

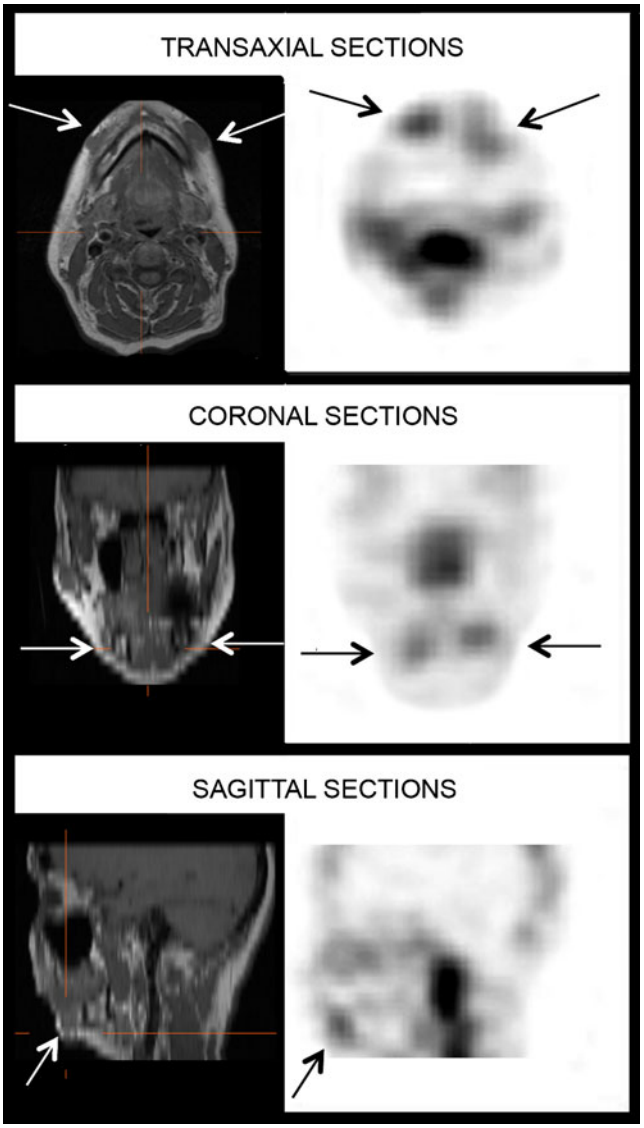

Fig. 4 Transaxial, coronal and sagittal MRI (fat-suppressed) and SPECT images in patient 9 (MR) 3 h after WBC injection. The filler is easily detectable in the MRI images and shows positivity in the WBC scintigraphy images (*arrows*)

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(L-lactic 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. 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 later might 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 of WBC 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/B_{early} equal to T/B_{late}). 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 half-life 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.

Conflicts of interest None.

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