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CASE REPORT

Macrolane injections for breast enhancement in undiagnosed breast malignancy: A case report

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KEYWORDS
Macrolane;
Breast Cancer;
Hyaluronic acid;
Lobular

Summary We report a case of cosmetic breast enhancement with Macrolane injections in an un-diagnosed breast cancer. This delayed cancer diagnosis and complicated surgical resection and reconstruction. It should therefore be mandatory for clinicians to exclude breast malignancy with imaging prior to Macrolane injection.

Case report

A 45-year-old nurse with family history of breast cancer underwent injections of 100mls of Macrolane into her breasts by a trained clinician. Prior to administration, skin tethering was noted by the attending clinician, however no action was taken to investigate this. Following Macrolane injections the tethering improved, though subsequently worsened. Four months after the Macrolane injections, she was referred to a breast specialist.

Examination in the breast clinic revealed a diffuse firm area below the nipple areolar complex. She underwent imaging with mammography, ultrasound scan, and MRI. The mammogram showed a spiculate area of increased density with in-drawing of the skin, as well as multiple cystic opacities (Figure 1). Ultrasound revealed a 1cm irregular hypoechoic mass consistent with malignancy. Core biopsy of the lesion confirmed lobular carcinoma. MRI was required to evaluate the extent of the mass and showed the tumour extending over 2 cm, surrounded by cystic areas.

Macrolane was visualised in both breasts with imaging, and had radiological appearances of simple cysts.

The patient underwent left mastectomy and sentinel lymph node biopsy. Identifying the extent of Macrolane injections at the time of surgery was impossible, and the planned implant reconstruction at the time of mastectomy was abandoned. Histopathology confirmed an invasive grade 2 lobular carcinoma (Figure 2). Macrolane present in the adjacent breast tissue was thought to be a benign mucocele-like tumour. Resection was complete at all margins and axillary lymph nodes were free of malignancy.

The patient has since undergone delayed left breast reconstruction with expander as well as right sided mastopexy.

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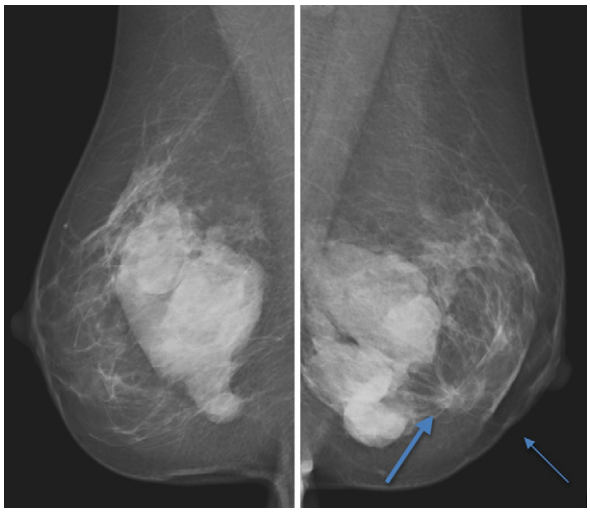

Figure 1 Mediolateral oblique views of the left and right breasts. The large arrow points to the spiculated tumour, and the small arrow to the skin tethering. The large, well-defined opacities in both breasts is Macrolane.

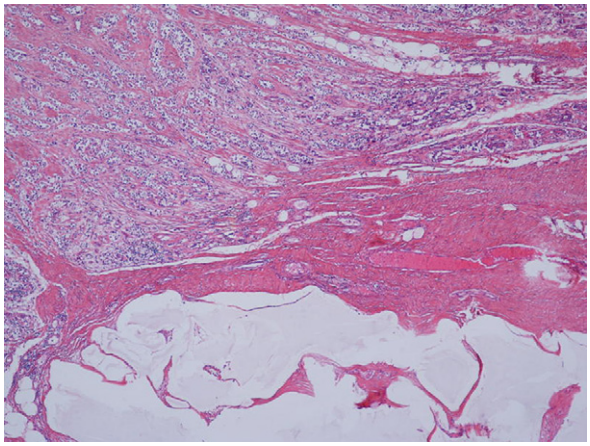

Figure 2 Histological slide of the specimen showing grade 2 lobular carcinoma.

Discussion

Breast cancer may present itself as a palpable lump or may be completely sub-clinical being diagnosed on screening mammograms. In this patient, Macrolane masked the malignancy clinically, delayed diagnosis and complicated the management.

Macrolane (Q-Med, Uppsala, Sweden) is a hyaluronic acid based gel used as a biodegradable tissue filler. It was approved in Europe in 2006 and is marketed for breast enhancement, buttock augmentation, and calf shaping.[1] Macrolane has the advantage of being minimally invasive, requiring local anaesthetic for administration. This also means there is minimal to no scarring post procedure. It is also non-permanent, and effects last for up to a year.[1]

Macrolane distorts the normal architecture of the breast, and therefore makes examination for breast cancer screening unreliable. It also makes self-examination more difficult as well as interpretation of breast imaging. Heden P et al revealed a 30% capsular contracture rate at 6 months post Macrolane injection.[2] This distortion not only complicates clinical examination and investigation of breast cancer, but also reduces delineation during surgical treatment of the tumour.

Teaching point

It should be mandatory for clinicians considering breast enhancement with Macrolane injections to screen their patients with a mammogram (>35yrs old) or ultrasound scan (<35 yrs old) prior to Macrolane treatment to exclude underlying breast malignancy.

Funding

None.

Conflict of interest

None.

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Macrolane injection

The ro

Macrolane™ injections provide immediate temporary cosmetic effect with low risk; the non-invasive procedure takes 15 minutes with minimal scarring and recovery time. On the surface it appears to be the perfect cosmetic treatment but is it too good to be true?

Introduction

Macrolane injections initially cost approximately £2000, however, with top ups necessary every 12-18 months the overall cost may be much higher than those with traditional breast implants. As with any procedure there are possible complications associated, with long-term risks not yet discovered.

With 9418 breast augmentation procedures performed in 2010[1] and the recent controversy surrounding the poly implant prostheses (PIP implants), there is ever-increasing demand for minimally-invasive techniques.

This article aims to discuss the advantages of Macrolane injections and the possible complications and concerns associated, focusing in particular in the role of breast imaging and breast management.

What is Macrolane?

Macrolane is a biodegradable gel based on hyaluronic acid (HA), found naturally within the human body, and necessary in the developmental process. However, HA is very metabolically active[2], lasting a short-time (minutes to weeks) and therefore, requires stabilisation to last longer.

A Swedish company known as Q-MED created and patented this stabilisation process, known as NASHA™ technology[3]. The NASHA technology was first used in a product called Restylane™, with safety efficacy well documented in over 14 years of application in facial aesthetics. After encountering success with Restylane, the technology was evolved to create Macrolane in 2007, a thicker substance with clinical uses, including corrective filler for deformities.

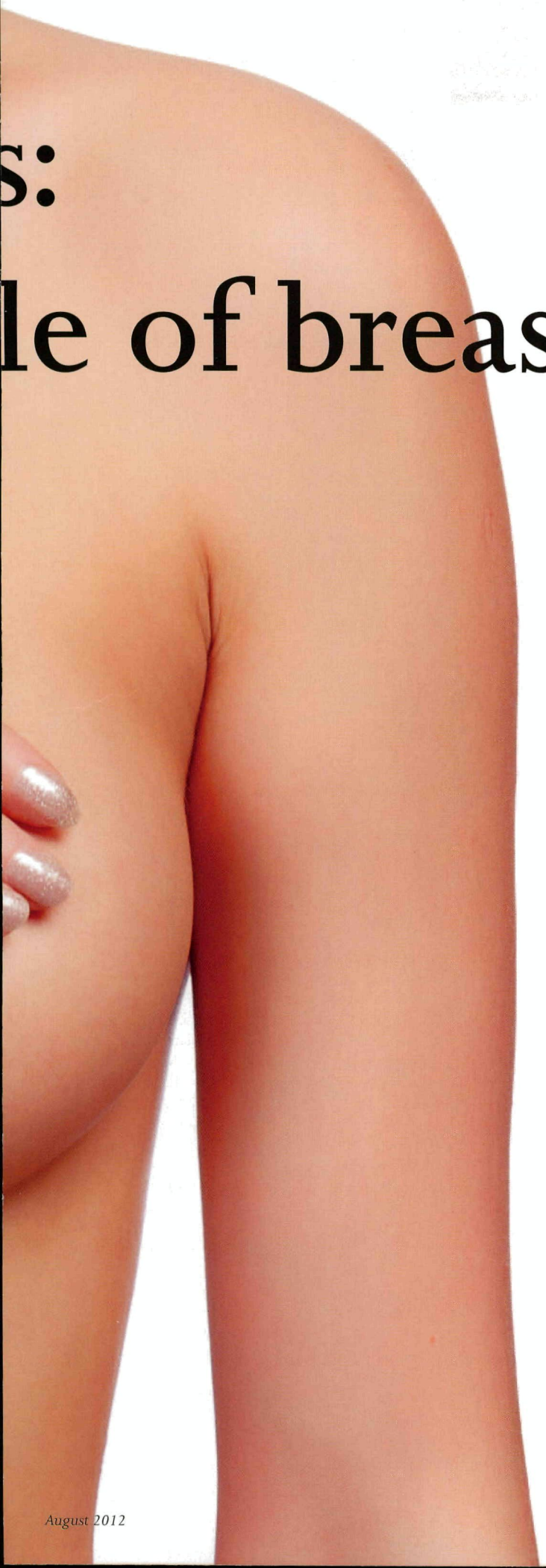
There are currently two versions of Macrolane available on the market: VRF20 intended for superficial subcutaneous injection and VRF30 used for deep subcutaneous administration.

Alternative breast augmentation

There are two types of breast enhancement: encapsulated and non-encapsulated. Encapsulated fillers such as silicone implants offer long-lasting correction, creating substantial volume, however disadvantages include the risk of rupture, cost and invasiveness of the procedure[4]. The history of encapsulated fillers has been controversial; Trilucent implants were removed in 1999 by the Medicines and Healthcare products Regulatory Agency (MHRA), due to the concern the soybean-oil filler could degrade into a genotoxic carcinogen and cause severe inflammation if ruptured[5].

Consequently hydrogel implants were discontinued due to possible pathological changes induced by the filler[6].

Non-encapsulated fillers are based on liquid and semi-solids requiring injection, including paraffin, injectable silicone and fat. These have various complications including migration, inflammatory reactions and granuloma formations[4]. Injectable silicone



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was first described in 1899 for the reconstruction of a scrotum; however, the long-term efficacy is questionable with little empirical evidence regarding safety to be found.

Fat is durable and versatile although recent study states fat survival post implantation is disappointing[3] there may be potential by altering harvesting methods and placement[7].

The history of implant regulation has proven to lack efficacy and safety standards have been compromised in some cases. The most recent concern regards PIPs, which contain industrial grade silicone and may be linked to anaplastic large cell lymphoma[8].

If the advantages of the non-encapsulated fillers are maintained, whilst complications reduced, the ideal cosmetic enhancement may be possible for the breast.

Procedure

An injection of 80-100ml of Macrolane is administered in order to increase the breast size by up to one cup, following local anaesthetic. The gel is ideally distributed between the breast parenchyma and pectoralis-major muscle.

A single treatment lasts approximately 12 months according to the manufacturer Q-MED, but a pilot study of MRI scans showed only minor degradation between three and twelve months, suggesting unlike smaller volumes, larger volumes of Macrolane may remain in the breast for an indeterminate amount of time[3]. A study of 12 patients reported indeterminate masses remaining in situ after two years[9].

The cost of Macrolane is comparable to a surgical implant after approximately three to four touch-ups[10], and although expensive, it is marketed as an alternative for those uncertain of a surgical outcome.

Clinical evidence

A Japanese study in 2006[11] gained EU approval attempting to trial the new NASHA technology by conducting injections within the breasts of 1100 patients using non-animal based hyaluronic gel. However the study used Restylane Sub-Q™ indicated for facial aesthetics and has a different consistency to Macrolane. Although the trial involved a large subject number, there is no reference to follow up or long-term outcomes as a result of the trial. Capsular contracture has been referred to as a complication however not discussed, nor the effects on breast screening, although it is suggested HA may delay the diagnosis of breast cancer.

CE mark of approval was granted in 2006 on the basis of a facial study using Restylane for lips and an unfinished study using Macrolane in the breasts of 24 people, with no long term effects established[12]. NASHA gels including Macrolane are legally licensed as an implantable medical device and not medicine, so do not require testing or monitoring. Despite CE approval, MHRA does not recommend the device as they depend on retrospective data.

Unlike Restylane, Macrolane has not received FDA* approval yet, as this requires many years of rigorous procedures investigated independently and clinical

performance data.

Macrolane indications include restoring deformities as a result of trauma, disease or congenital defects, and aesthetically shaping contours. A recent article discusses the successful use of Macrolane to treat chest concavity[13], however, no long-term outcomes are established. There is currently no literature discussing Macrolane for postoperative breast-reconstruction.

High levels of patient satisfaction using Macrolane for breast augmentation have been noted soon after treatment[3].

Concerns

In 2011 the French Agency for Safety of Health Products announced the disuse of Macrolane for breast augmentation, despite over 20 countries approving, including the UK. This decision was based on four principles including: an increased risk of inflammation due to repetition of procedure, several reports of capsular contracture, changes to breast anatomy resulting in delayed diagnosis of breast disease and most importantly the public health priority of early-diagnosis of breast cancer[14].

There is no established link between Macrolane and cancer[15], however, the statistics that one in eight women will develop breast cancer within their lifetime, would make any direct-link between breast cancer and Macrolane difficult to determine. However, there is controversy about the influence HA may have on the progression of cancer[16]. The interaction of HA and its cell receptor CD44 promotes cell proliferation, invasion and angiogenisis, with increased levels found present in breast-cancer patients[17]. Increased HA may directly influence patient survival as an independent prognostic indicator[18]. Failure to remove HA through normal hyaluronidase-enzyme activity is thought to promote malignant growth[19].

Macrolane may delay diagnosis, especially if cancer is not excluded prior to treatment, as in the case of a 45 year-old female with family history of breast cancer who underwent treatment, despite the administrating physician noting skin tethering. The patient was referred to a breast-specialist after the tethering worsened four months post-injection. Imaging showed multiple cystic opacities and a spiculate area, confirmed as lobular carcinoma after biopsy (figure 4). Prior screening is advised with mammography and ultrasound, whilst high-risk patients should not undergo treatment[20].

Despite recommendations, this case indicates the failure to exclude pathology prior to treatment, and the irresponsibility of treating patients with a family-history. There was lack of breast cancer awareness by the clinician and a failure to investigate current symptoms. Practitioners of Macrolane are advised to register to the Independent Healthcare Advisory Services (IHAS), however, it is not an enforceable regulation.

Possible complications from Macrolane injections

Complications vary in severity, and are indicated in the consent form used prior to treating patients with Macrolane (see figure 1).

An unpublished study found that 16 of 20 women reported 44 adverse events, with four patients diagnosed with capsular contracture[12], whilst another study of 194 women reported adverse events in 21.1% of which 8.7% were considered to be major[16], therefore these complications require further investigation.

Migration

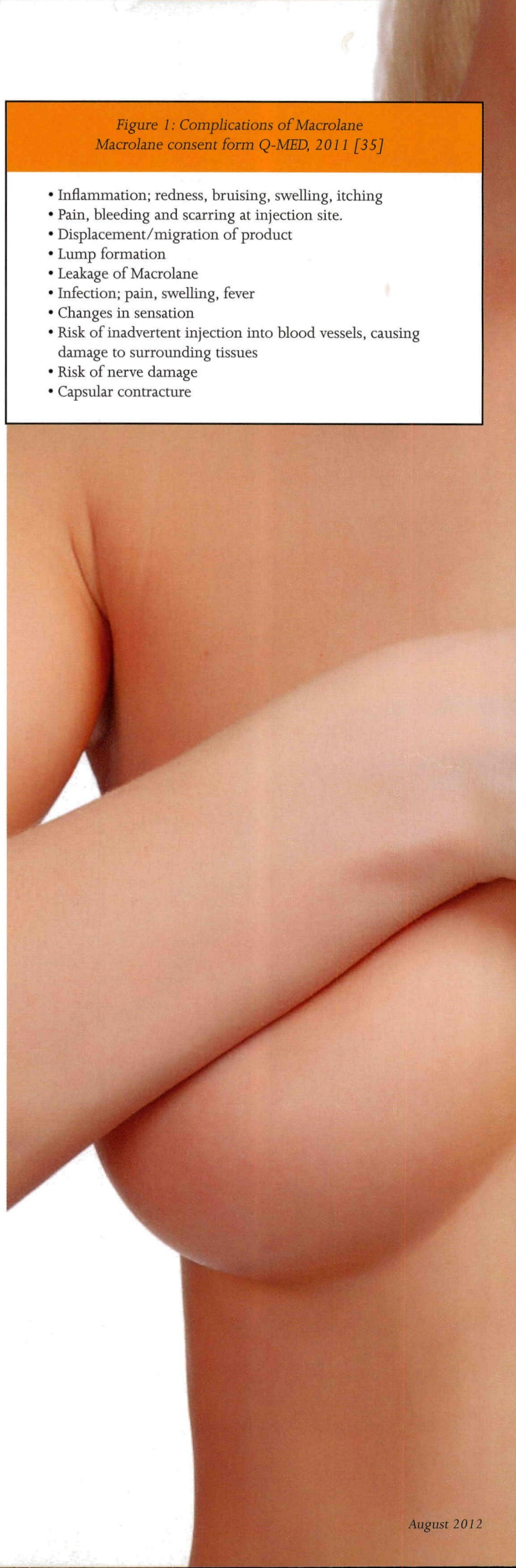
A study using 320 patients in two groups, found fewer complications encountered with a single-deposit injection under ultrasound-guidance[21]. Patients having multiple-deposits suffered migration and lumps. However, the study involved changing both injection-technique and imaging guidance variables, and failed to follow-up all patients.

Ultrasound-guidance is required for accurate placement based on three further cases, where Macrolane migrated to mammary tissue and pectoralis major muscle with some lasting effects such as paraesthesia and palpable lumps 18 months post-injection[22]. Despite this, Q-MED licences the product for use without imaging support.

Placement is crucial as migrating Macrolane into the glandular tissue decreases the sensitivity of breast imaging; however even with the improved single injection-technique migration is possible as the product follows the path of least resistance[23].

Figure 1: Complications of Macrolane Macrolane consent form Q-MED, 2011 [35]

- Inflammation; redness, bruising, swelling, itching
- Pain, bleeding and scarring at injection site.
- Displacement/migration of product
- Lump formation
- Leakage of Macrolane
- Infection; pain, swelling, fever
- Changes in sensation
- Risk of inadvertent injection into blood vessels, causing damage to surrounding tissues
- Risk of nerve damage
- Capsular contracture



Although migration is regarded as a minor-complication, it is often associated with pain and lumps resulting in anxiety, especially affecting self-breast awareness.

Hyaluronidase can be injected to remove HA. A study of 207 patients reported 47% had multiple lumps with seven undergoing aspiration[21].

There has been success with hyaluronidase for facial correctness[24], however, frequent localised allergic reactions have been reported[25], and the recommended dosage is yet to be determined to effectively correct Macrolane lumps. Although often remedied, breast lumps are a recognisable symptom of breast cancer and investigation may lead to triple-assessment involving biopsy, and even surgical exploration.

Capsular contracture

A common complaint of treatment is capsular contracture, which is caused when a foreign-body reaction occurs resulting in hardened fibrous tissue around the substance.

A case study involving a 62 year old female noted multiple pockets of Macrolane with individual fibrous capsules[26]. The effect of capsular contracture can become lumpy and painful, often requiring intervention.

The study concluded capsular contracture is due to inaccurate infiltration of filler into the pectoralis muscle, however, a more recent study indicates patients undergoing Macrolane for pectoralis reshaping found no problems, confounded by an ongoing clinical-trial of Macrolane for gluteus enhancement[27].

Closed capsulotomy through massage is used to break up the hardened product, however, if this fails, manipulation with a cannula, or aspiration with an injection of hyaluronidase is used to remove the substance[28].

Allergic reactions

Unlike similar fillers which use a highly crosslinked procedure which is foreign to the body, the NASHA technology modifies the HA less than 1%[28]. Therefore, as Macrolane is based on non-animal HA, the theory suggests there is no risk of allergic reaction if injected.

However, a study using HA as a facial-filler stated 24 of 70 patients experienced injection-site reactions, including infection, bruising, pain and bleeding[29]. A possible cause of hypersensitivity may be related to impurities caused from the bacterial fermentation process[4].

Although Q-Med does not advise skin-testing, a study revealed four out of five patients tested positive for intradermal skin reactions approximately eight weeks post injection[30], and further studies are warranted. It is unknown how testing would influence the number of treatments conducted.

Long term effects

The available reports documenting cases of complications appear to contain a limited number of subjects, with changing variables and minimal follow-up. Much research has been conducted by Q-MED, however, focusing on the NASHA technology and not Macrolane itself. Further studies are warranted to determine the best technique, providing consensus between practitioners.

There is currently a multi-centre retrospective study being conducted to evaluate the long-term safety of Macrolane in female breasts[31].

The role of breast imaging

The Q-MED Macrolane website information is careful to stipulate the well-tested safety and efficacy clinical-use of NASHA gels. 'NASHA technology has been used in over 10 million aesthetics worldwide'[28], but this refers to the facial area using Restylane, they do not say they are well tested for the breast. Many of the clinics that advertise Macrolane for breast state Macrolane does not 'affect' or 'interfere' with the mammogram, however this is often carefully worded, as in effect Macrolane does not prevent the mammographic procedure, but the information often makes no reference to the interpretation of the mammogram.

A study was done using 19 patients post Macrolane treatment, who underwent medio-lateral oblique mammography and MRI at three, 12 and 24 months[32]. Only five of the 19 patients underwent mammography, as they were over 35. All five patients had glandular tissue obscured by the Macrolane; this has the potential to disguise pathological lesions. The same author's recommendations in

Keywords
- Macrolane
- Hyaluronic acid
- Breast augmentation
- Mammography
- Breast filler

Learning outcomes
- What is Macrolane™ and how is the procedure conducted?
- What are the concerns and potential complications?
- How does Macrolane affect breast imaging?
- What are the recommendations for imaging breast treated with Macrolane?

another study indicates US should be used in conjunction with mammography as this provides the same sensitivity and specificity as mammography alone for breasts without Macrolane[33].

In our own experience US showed no valuable data at all, as the gel distributed irregularly and was indistinguishable from cysts. Although there is improvement in visualisation when compared with a silicone/saline implant, tissue is greatly reduced when compared to no implant at all (see figure 2).

Macrolane on ultrasound often demonstrates anechoic collections with internal echoes described as the 'sparkly lake sign', but can occasionally be misdiagnosed, for instance as abscesses (see figure 3). Although the collections are well defined, there are often channels connecting the multiple deposits used to differentiate from cystic lesions[23].

Aspirations may be difficult due to solidifying Macrolane, and multiple needle insertions are required due to extensive collections, therefore ultrasound-guided biopsies are needed furthering anxiety to the patient.

If imaging is indeterminate, magnetic resonance imaging (MRI) to identify pathologies is recommended[23]. Imaging should be performed at day 6-14 of the menstrual cycle in order to minimise false-positives due to enhancement of normal parenchyma. Macrolane appears as areas of low T1/high T2 signal, consistent with a complex cyst. Contrast medium provides rim-enhancement of Macrolane, useful for accurate sampling if histology is needed, although not performed routinely.

Microcalcification proves consistently difficult to evaluate without biopsy under stereotactic-guidance, and unfortunately is often a by-product of capsular contracture, therefore this may pose a problem for breast screening even after the Macrolane product has completely degraded[34]. Long-term studies may provide information regarding the link between microcalcificaton and Macrolane.

It has been recommended that radiologists become more familiar with the imaging appearance of Macrolane, and suggest referring patients to reference radiologic centres[10], although these have yet to be recognised, as many centres have limited experience.

Recommendations

Research indicates Macrolane fillers provide diagnostic challenges; therefore it is important we are aware of how best to handle this type of patient. Recommendations are based on our own experience and advice from the manufacturer of Macrolane, Q-MED.

It should be standard procedure to ask all clients undergoing breast imaging if they have ever had filler injected into their breasts.

Clients who have a history of Macrolane fillers are advised to attend a static unit to have their mammogram under radiologist guidance; bringing any information they have with them (indicated in the invitation letter).

A qualified radiographer should use digital equipment to perform a standard mammogram, only after the risks and limitations of the procedure are explained to the client. Q-Med advises a written consent form is required similar to implants; however, some units currently do not do this.

Compression may be applied as normal according to Q-MED; however, this is at the radiographers' discretion. It is our own protocol to perform a single view using minimum compression to establish if capsular contracture has taken place.

Exposure will vary according to the amount of Macrolane remaining in situ, although manual exposure may be set if necessary.

Ultrasound is often used in addition to mammography, and MRI may be used for problem-solving, with or without contrast enhancement. It is important information gathered on the appearances of Macrolane is shared between units to gain further understanding of the various anomalies.

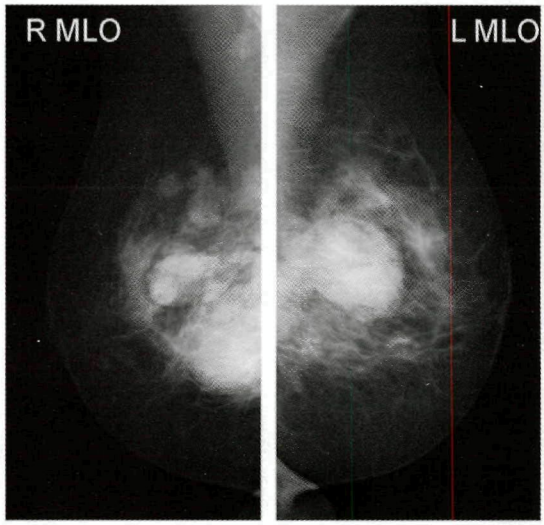
Conclusion

Macrolane injections have many advantages and may have their place in the minimally invasive breast augmentation market, however further clinical studies are required to establish the long-term effects.

Research suggests the link between hyaluronic acid and cancer requires further investigation. Despite minor modification there is still an element of a foreign substance introduced where it does not naturally occur, posing the question: Is it dangerous to modify a structure from within the body using a chemical process to then

Figure 2: Examples of two patients post-Macrolane injection – MLO mammography (Pienaar et al, 2011) [23]

Macrolane filler appears as defined focal densities within breast parenchyma.



Macrolane filler within the pectoralis muscle resulting in bulging appearance.

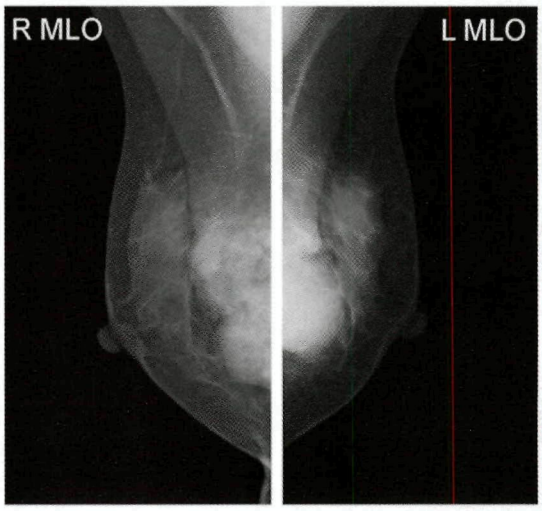
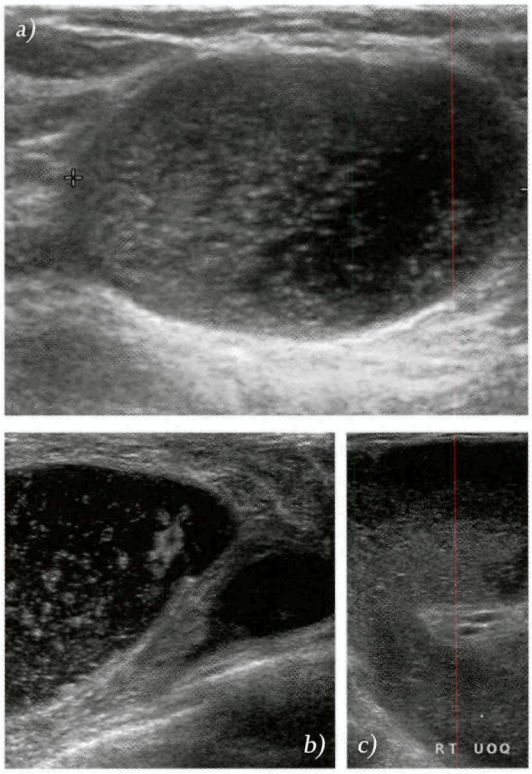


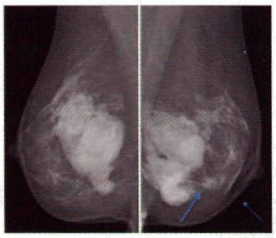
Figure 3: 'Sparkly lake sign' (Pienaar et al, 2011) [23]

a) Large anechoic area with internal echoes.



b) Multiple collections of Macrolane.
c) Abscess with similar appearances to Macrolane.

Figure 4: Case study showing breast cancer and Macrolane on MLO mammography (Crawford and Shrotria, 2011) [20]



Mediolateral oblique views of the right and left breasts. The large arrow points to the spiculated tumour, and the small arrow to the skin tethering. The large, well-defined opacities in both breasts is Macrolane. Image courtesy of Elsevier BV.

reinsert it? The answer is yet unknown.

Although there are known complications, as with any filler, the benefits must outweigh the potential risk of complications in order to be successful. Patients undergoing treatment should be aware of the implications of Macrolane to delay the diagnosis and treatment of malignant changes within the breast.

It is imperative a thorough clinical and family history is established and underlying pathology excluded prior to treatment.

Breast screening is a public health priority within the UK and regardless of the economic incentive to encourage breast augmentation, first and foremost as healthcare professionals we must ensure the safety of the public.

Although a major clinical trial is underway, it is important more information is published on the long-term outcomes of Macrolane using larger numbers of subjects.

Macrolane presents many diagnostic challenges within the breast, which are likely to compromise patient-care. Migration may result in obscuring glandular breast tissue, concealing underlying pathologies, although technique improvement may improve this. Capsular contracture is often easily remedied, but implications of increased fibrous tissue and microcalcification remaining even after complete degradation may prove challenging.

A thorough history prior to imaging is essential as clients may not be aware of the lasting effects of Macrolane within the breast.

Although breast units currently have limited experience in imaging and interpreting Macrolane, statistics suggest there will be an increase in this procedure in the future. It is therefore necessary that radiology departments understand the anatomical variants and pathological changes that may occur as a result of Macrolane injections, by sharing their individual findings with the greater field.

Addendum

Recently, Q-MED, the manufacturer of Macrolane, has withdrawn the promotion of Macrolane for breast enhancement[36]. Although treatment worldwide for breast enhancement has been discontinued, Macrolane is still available for body contouring procedures.

The decision is not due to safety concerns, however, but the failure of consensus between radiologists regarding best practices post treatment, including breast-examination and mammography interpretation.

Mammography practitioners should be aware of the reasoning behind the withdrawal of the treatment for breast augmentation using Macrolane, and also the associated radiological implications of those already treated.

* US Food & Drug Administration

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References for this article can be found under 'Synergy resources' at *http://www.sor.org//learning/library-publications/synergy*

This article has been prepared following local guidance relating to the use of patient data and medical images.

To comment on this article, please write to *melaniea@synergymagazine.co.uk*

Accreditation by cpd now the College of Radiographers

How to use this article for CPD

CPD Thoughts

- Describe the concerns associated with Macrolane
- Discuss the implications of Macrolane on breast imaging
- What are the recommendations for imaging Macrolane?
- Discuss how you will implement a protocol for Macrolane in your breast unit.

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CORRESPONDENCE AND COMMUNICATIONS

Macrolane is no longer allowed in aesthetic breast augmentation in France. Will this decision extend to the rest of the world?

Sir,

In recent years, the market for resorbable fillers has been steadily expanding. In France, the European Community's (EC) seal of approval is sufficient for distribution. Approval from the AFSSAPS (French Agency for Safety of Health Products), the French equivalent of the US Food and Drug Administration (FDA), is not required to market resorbable fillers, because they are considered to be "implantable medical devices" and not drugs. Macrolane (Q-Med AB, Uppsala, Sweden) is a NASHA (Stabilized Non-Animal Hyaluronic Acid) gel-based technology and has been available on the French market since 2007 as a filler that can be used in all areas of the body except the face. It is highly crosslinked, and this property slows its absorption into the body but can also leave long-lasting residues. At the end of 2008, Macrolane received EC approval for use in breast augmentation.

Macrolane is currently approved in more than twenty countries but has not been approved by the US FDA. The absence of controlled clinical trials, as noted by Nahabedian, quickly raised questions.[1] The primary published studies were conducted by Per Heden, a Qmed consultant.[2] Since 2008, however, several independent publications have reported problems following the injection of Macrolane into the breast. Crawford et al. have recently reported a case of delayed breast cancer diagnosis due to masking of the tumour by injections of Macrolane in the breast.[3]

On August 26, 2011, the AFSSAPS decided, in accordance with article 14ter of European directive 93/42/CEE, that Macrolane would no longer be approved for use in aesthetic breast augmentation.[4] The AFSSAPS made this decision following four principal arguments reported in the recent literature.[3,5]

First, the use of an injectable medical device for breast augmentation requires repeated invasive procedures. This may cause undesirable inflammation in the breast tissue, leading to an increased risk of cancer. Second, there are risks associated with injecting a mobile product into the breast, including nodule formation due to fragmentation of the product and a high incidence of capsular contracture. Third, perturbations in the breast anatomy can change physical examination findings and affect the interpretation of breast imaging, possibly causing delays in the diagnosis of breast disease, as reported in recent publications. Fourth, screening and early diagnosis of breast cancer is a public health priority.

In addition, this restriction will apply not only to Macrolane but also to all fillers for breast augmentation that appear on the market in the future. Following this decision, the benefits and risks of breast injections of hyaluronic acid should be reconsidered. It is certain that this decision will change many providers' practices. The precautionary principle has been applied in France, and it is possible that in the coming months, other countries will do the same, both in the European Community and elsewhere in the world. Ultimately, a long-term, prospective controlled study should be undertaken to demonstrate the safety of these types of breast injections before considering new indications.

Conflict of interest

None.

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Discussion: Macrolane is no longer allowed in aesthetic breast augmentation in France. Will this decision extend to the rest of the world?

Sir,

I would like to respond to the correspondence and communication submitted by Chaput et al.[1] regarding the decision of the French Agency for Safety of Health Products (AFSSAPS) to no longer approve Macrolane™ (Q-Med AB, Uppsala, Sweden) and other fillers for aesthetic breast augmentation.

Having been subjected to the Poly Implant Prothèse (PIP) scandal with silicone breast implants containing non-authorized silicone gel, it is understandable that the AFSSAPS takes on a more precautious view on aesthetic breast augmentation in France. I respect the views and concerns expressed by Chaput et al.[1] However, they have not reviewed the clinical data from the studies on Macrolane, and the principal arguments conveyed in support of the decision need to be discussed further.

Firstly, there is indeed an increased risk of undesirable inflammation in the breast tissue following invasive procedures. It is the opinion of Chaput et al.[1] that injection of Macrolane will cause more inflammation than more invasive breast implant placement, but no data to support this concern was provided. To my knowledge, long-term follow-up of thousands of patients who have received permanent breast implants has not shown an increased risk of breast cancer deaths as a result of trauma or inflammation from breast surgery. According to my clinical experience, it is not uncommon that patients who have had one or two treatments with Macrolane request permanent silicone implants. In these patients, the Macrolane acts as a "door opener" building the confidence the patients need to decide for the procedure. In all of these patients, any remaining Macrolane has been easy to remove and a biopsy of the capsule and adjacent gland has been taken. In the histological examination, none of these cases has had any signs of inflammatory reactions. The capsule is very similar to the capsule seen around traditional silicone implants, and no morphological changes in the gland have been noted.

Secondly, post-injection fragmentation does not occur with Macrolane, rather, my clinical experience is that the product is degraded and that possible mobility of the product can be prevented by using the correct injection technique. When injected as a single cohesive implant as recommended in the Instructions for use of Macrolane, the risk of complications such as lumps in the breast is much reduced compared with when Macrolane is injected as multiple deposits.[2] Lumps in the breasts were reported for a total of 47% of the patients who had Macrolane injected as multiple deposits, compared with for 13% of the patients who had Macrolane injected as a single cohesive implant, and the vast majority of the lumps had disappeared within 30 days of treatment. Magnetic resonance imaging (MRI) performed repeatedly over 24 months after treatment clearly shows that the product stays as a cohesive implant (Q-Med data on file). Any capsules that arise are also easily managed and treated.[3]

Thirdly, perturbations of the breast anatomy may result following use of fat injections and permanent implants, and are thus not specific for treatment with Macrolane. That said, the challenges of interpreting mammographic films of breasts treated with Macrolane are similar to those of naturally dense breasts and those of other breast implants. However, ultrasound is suitable for examination of Macrolane-injected breasts,[4] and simply performing an ultrasound in addition to the mammography will likely provide an adequate basis for diagnosis of any breast malignancies prior to treatment (Q-Med data on file). In addition, MRI may also be performed as needed, but has the drawbacks of high costs and high frequency of false positive results.

Fourthly, I completely agree that screening and early diagnosis of breast cancer is a public health priority. Therefore, a thorough breast examination must be performed prior to every breast treatment, may it be with Macrolane or any other implant. Regarding the case of delayed breast cancer diagnosis reported by Crawford et al.,[5] the presence of skin tethering prior to Macrolane treatment indicate that the patient most likely already had breast cancer prior to treatment, and the case further highlights the importance of performing a thorough breast examination prior to any treatment.

In conclusion, it is of utmost importance to continue to perform studies with Macrolane. To my knowledge, additional safety data will be available from ongoing studies, one of which is currently being conducted at my own practice as well as in France. In the mean time, it is important to keep in mind that there are several benefits with injectable implants compared with performing surgery to insert permanent implants. Injectable implants are less invasive, can easily be removed by aspiration, and

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Macrolane™ Injections for Breast Enhancement and Clinical Imaging

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Wrightington, Wigan and Leigh Foundation NHS Trust

Introduction

Macrolane™ injections are injectable fillers used for breast enhancement since 2007. However, recently Macrolane has been discontinued for this purpose due to lack of radiological consensus when reviewing the clinical breast.

Macrolane can result in anatomical variants and misunderstood pathology in treated breasts leading to clinical challenges affecting breast imaging, including mammography, ultrasound and magnetic resonance imaging (MRI).

Macrolane™
Gracefully shapes your body

Hyaluronic acid is found naturally within the body but requires stabilisation for temporary enhancement (approx. 12 months). This stabilisation process uses a new technology developed by the manufacturers of Macrolane and is know as Non-animal Stabilised Hyaluronic Acid (NASHA).

Procedure

Macrolane (approx. 100ml) is injected into each breast using local anaesthetic. Enhancement of up to one cup size is obtained in around 30 minutes, with minimal scarring and side effects.

Complications

Symptomatic pain and lumps often require investigation and may prevent self-breast awareness, resulting in delayed presentation. Migration of the filler may obscure underlying pathology in breast parenchyma, and pectoral region.

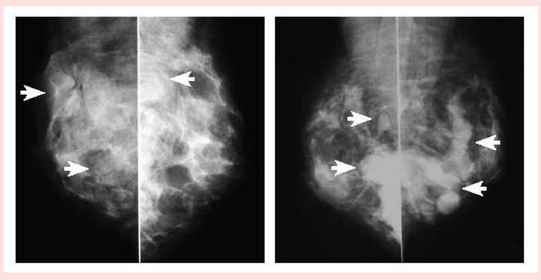

Figure 1: Mammograms (MLO projections) of two patients with arrows indicating Macrolane™.

Capsular contracture and fibrosis occurs when the body reacts to a foreign substance and may result in multiple hard lumps forming around the individual deposits.

Macrolane is a temporary filler designed to degrade naturally and become reabsorbed. However, a by-product of degradation is micro-calcifications which may remain in the breast long term.

The British Association of Aesthetic Plastic Surgeons recently conducted a survey (2012) reporting 1 in 4 surgeons have already seen complications from Macrolane.

Clinical Imaging

Macrolane increases the overall density of the breast tissue on mammography, whilst the individual deposits can appear as multiple focal densities, often confused with cystic lesions.

The manufacturers recommend ultrasound be performed routinely to investigate areas of concern. Macrolane appears as anechoic lesions with internal echoes described as the ‘sparkly lake sign’ (see fig.2).

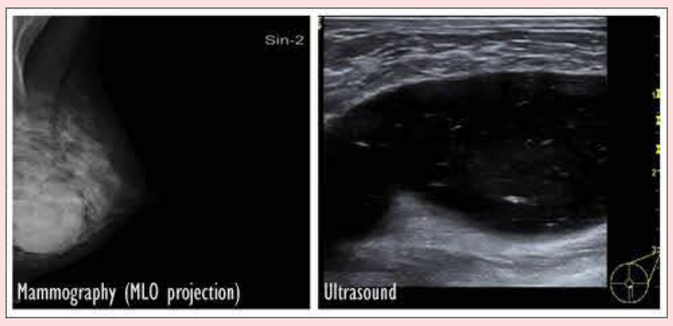

Fig 2: Mammography shows increased density and Ultrasound displays ‘Sparkly lake sign’.

Deposits of Macrolane are connected with interconnecting channels, due to the migration of filler into the surrounding tissue. The ‘Sparkly lake sign’ and channels are often unnoticed by those with limited experience and so imaging may prove inconclusive.

Assessment may require fine needle aspiration (FNA), which may prove difficult due to fibrosis of the deposits. Ultrasound core biopsy is then required to rule out malignancy.

MRI proves valuable when problem-solving (see fig.3) and in younger patients unable to undergo mammography.

Contrast medium provides rim-enhancement of the lesions and biopsies can be performed under MRI guidance.

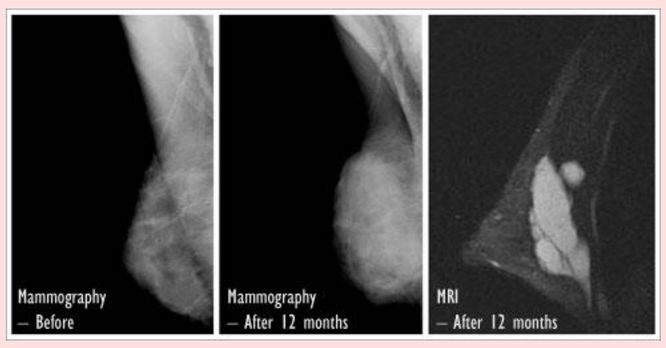

Figure 3: Mammography is inconclusive, however, Macrolane™ deposits seen on MRI.

However, MRI is time-consuming, expensive with limited availability. In addition, MRI is restricted to days 6-14 of the menstrual cycle to reduce false positives, incurring further patient anxiety.

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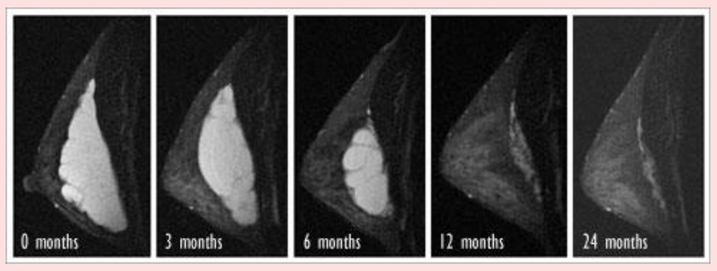

Figure 4: MRI shows normal degradation over 24 months

Degradation can vary between patients but has been found to last up to five years in some cases.

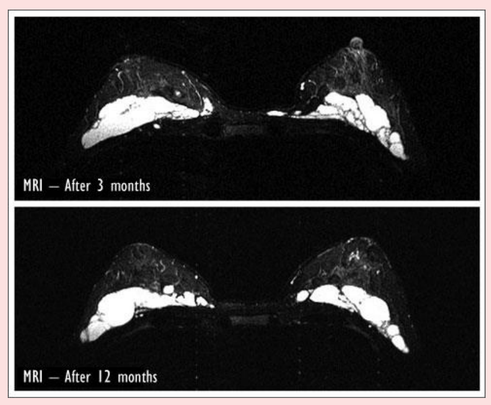

Figure 5: MRI scan 12 months post treatment demonstrates minimal degradation of Macrolane™.

Macrolane is detectable on mammography, ultrasound and MRI and has the potential to reduce the diagnostic quality of clinical imaging.

Recommendations

The following recommendations are taken from the manufacturers guidance, MHRA advice and our own protocol.

- Full history prior to Imaging
- Clients advised to bring any information along (e.g. Patient Treatment Card)
- Mammogram using digital equipment
- Radiologist guidance
- Explain limitations of mammography (similar to a breast implant)
- Single view mammography with minimal compression
- Mammography and Ultrasound combined
- MRI for problem-solving
- GP’s may wish to consider repeat referral

Conclusion

Thousands of patients have already undergone treatment in the UK, many of which, have yet to undergo routine breast screening. The long-term effects of Macrolane on the breast have yet to be established.

Macrolane may reduce the diagnostic quality of clinical imaging to varying degrees, whilst the increase of micro-calcifications found within the breast in those who have previously undergone treatment may impact the number of stereo-tactic core biopsies units perform.

Macrolane therefore has the potential to delay breast cancer diagnosis in those treated.

Delay in breast cancer diagnosis is a public health risk, therefore it is paramount we understand appearances on breast imaging.

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Radiological assessment of the breast following enhancement with Macrolane: Managing the challenges

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ABSTRACT

Macrolane VRF®, a biodegradable, stabilized hyaluronic acid gel, was used for breast enhancement 2008–2012. Similar to permanent implants, the presence of Macrolane gel may interfere with interpretation of mammography. This short communication aims to provide a guide to the appearance of Macrolane on radiology examination (including mammography, ultrasound and magnetic resonance imaging) and aid selection of the most appropriate imaging modality to facilitate breast examination in women who have undergone Macrolane breast enhancement.

1. Introduction

Macrolane VRF® (Q-Med AB, Uppsala, Sweden) is a biodegradable, stabilized hyaluronic acid gel indicated for use in volume restoration and contouring of body surfaces. Between May 2008 and April 2012, Macrolane was also marketed for breast enhancement. Typically, 100 mL Macrolane was injected in the space between the pectoralis fascia and the glandular tissue. The resorption rate varied between patients, but after 24 months, a mean of approximately 20% of the injected volume still remained in the breast [1]. Even after more than 4 years, small amounts of Macrolane were still visible on magnetic resonance imaging (MRI) or ultrasound in some patients [2]. The safety and performance of Macrolane in this indication has been documented [3–7]. Nevertheless, the breast enhancement indication was withdrawn by the manufacturer in April 2012 because of the potential for Macrolane to interfere with interpretation of mammograms for the purpose of breast cancer screening. This, in turn, may delay the diagnosis of breast lesions. Interference with interpretation of mammograms can also occur when imaging permanent breast implants [8].

Despite the withdrawal of the breast indication, several thousand women have already been treated. The possibility that some product could still be present in the breasts [7] prompts the need to disseminate knowledge on the product's appearance on radiological assessment of breasts following Macrolane treatment. To meet this need, a group of radiologists experienced in the imaging of this patient population and consultant plastic surgeons attended an expert meeting with the specific aim of discussing and describing the most appropriate imaging modalities for a woman treated with Macrolane in the breasts. This short communication summarizes data and images from radiological studies, as well as case experience of participating experts, to show the appearance of Macrolane on mammography, ultrasound and MRI.

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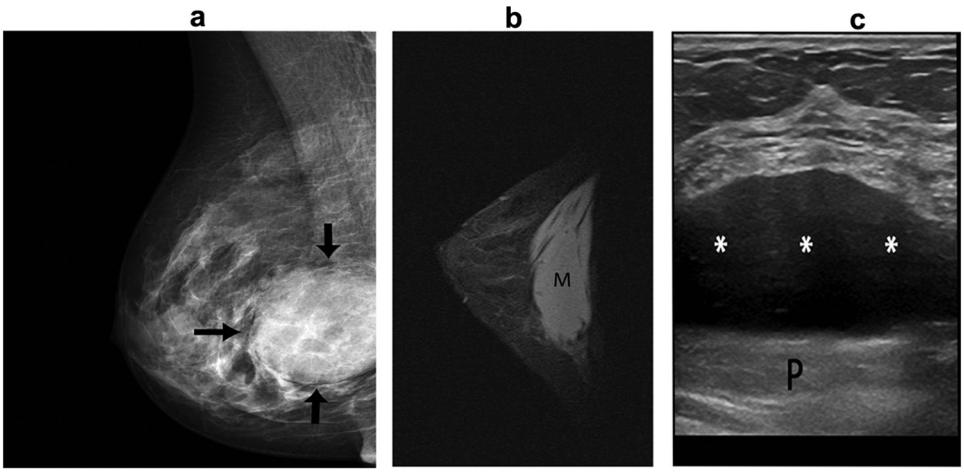

Fig. 1. (a) Appearance of Macrolane on digital mammography (right medio-lateral oblique [MLO] view): well-circumscribed mass (arrows) of low to medium density is seen. (b) Tbypical appearance of Macrolane (M) by MRI (using Sagittal Short TI Inversion Recovery [STIR]) 12 months after treatment. (c) Tcypical appearance of Macrolane by ultrasound (transverse close to the nipple) 12 months after treatment. Macrolane (*) superficial to pectoralis muscle (P) and deep to breast gland.

2. Rationale for development of recommendations

2.1. Ability to adequately visualize breast tissue using different imaging modalities following Macrolane treatment

Macrolane comprises 98% water and 2% hyaluronic acid and, as a consequence, has an appearance similar to water on all imaging modalities (see Fig. 1a–c for examples). On mammography, Macrolane can be seen as an area of increased density. On ultrasound, it can appear cyst-like, with anechoic features [9] or, in some cases, can contain punctate internal echoes described by Pienaar et al. [10] as 'the sparkly lake sign'. Macrolane is clearly visible on MRI, appearing as areas of low T1/high T2 signal, without contrast enhancement and similar in appearance to cysts. These lesion-like cysts do not enhance with intravenous gadolinium, therefore facilitating their differentiation from the malignant masses that are enhanced.

The Instruction for Use for Macrolane emphasised that the implant should be placed in a position that would minimize the risk of adverse effects and aid radiological evaluation. Ideally, Macrolane was to be placed as a single, implant-like deposit in the retroglandular space (see Figs. 2 and 3). Depending on the site of placement of Macrolane, the product has different appearances on mammography (see Fig. 4a and b). Diagnostic problems may arise if multiple deposits of Macrolane are present in the breast tissue because it may be difficult to differentiate Macrolane from breast lesions. Diagnostic problems may also arise because the gel can mask breast lesions, including cancer.

2.2. Concerns regarding use of mammography to visualize Macrolane

The use of mammography for breast cancer screening has limitations depending on the age group and breast density. A number of studies have looked at the sensitivity and specificity of mammography in different age groups and show that, in younger patients, and in those with particularly dense breast tissue, breast cancer is more difficult to detect using mammography [11]. It has been recommended that women with dense breasts should have whole breast ultrasound performed routinely to complete the screening procedure [12].

The adoption of digital mammography has led to superior image resolution and the opportunity to magnify or invert images, as well as to improve the detection of cancer in women with dense

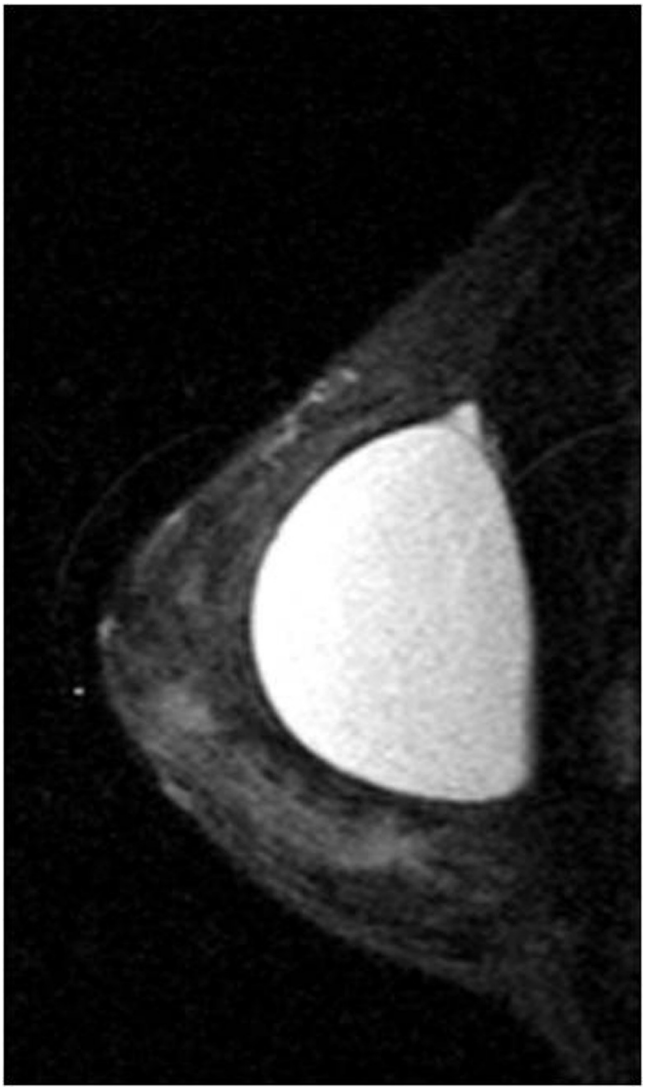

Fig. 2. Typical appearance of Macrolane following placement as a single implant (12 months post-treatment) on MRI (sagittal STIR).

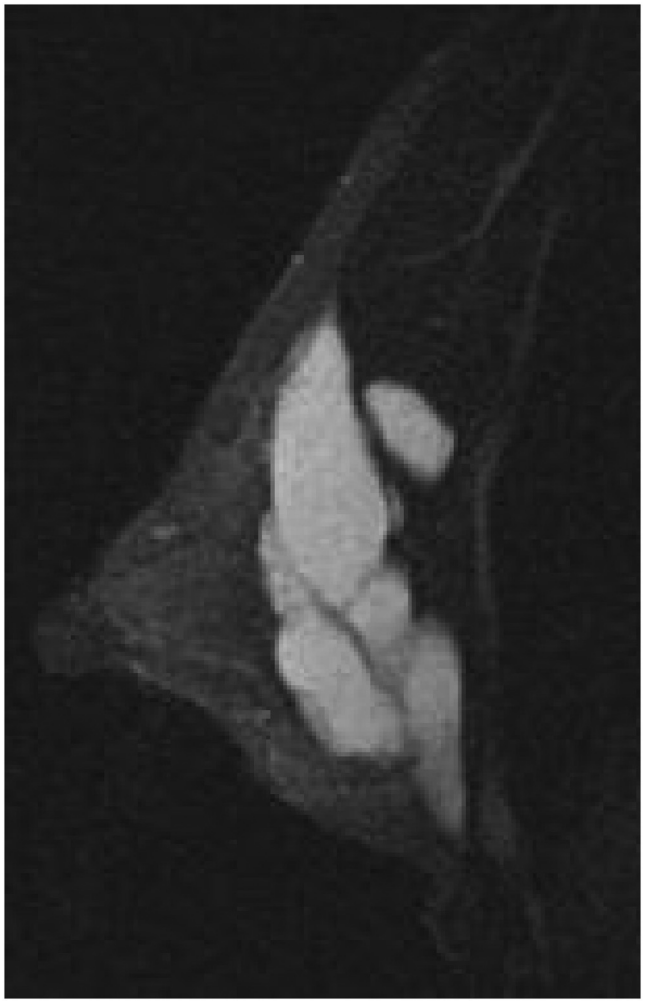

Fig. 3. Appearance of Macrolane as multiple deposits following re-treatment (6 months post-treatment) on MRI (sagittal STIR).

breast tissue [13,14]. But, even if digital mammography is available, the question regarding the adequacy of the modality to detect abnormalities in women who have been treated with Macrolane in the breast remains. A multi-centre study of 71 women undergoing breast enhancement with Macrolane in France and Sweden included an assessment of the product's interference with mammography and what additional radiological examinations might be required to provide a satisfactory examination [7]. Each woman had approximately 100 mL of Macrolane placed between the gland and the pectoral muscle in each breast and a sub-group of 22 subjects had re-treatment at nine months. All patients underwent digital mammography and ultrasound prior to treatment; followed by MRI for Macrolane volume measurement and digital mammography and ultrasound at 24 months. Imaging difficulties with Macrolane were evaluated in 30 subjects 24 months after initial treatment by two independent radiologists experienced in breast diagnostics. The radiologists concluded that the information provided by digital mammography alone at 24 months was only acceptable for screening purposes in up to 56% of cases in the single-treatment group, and in up to 40% of cases in the retreatment group. However, when digital mammography was supplemented with ultrasound of the breasts, acceptability exceeded 93% in both the single-treatment and retreatment group, suggesting that it is possible to evaluate the breasts in the vast majority of patients using a combination of digital mammography and ultrasonography examination.

2.3. Concerns regarding the masking of cancerous lesions

For all breast implants, there is a concern that the presence of implants might lead to a delay in detection of breast cancer. The potentially inadequate visualization of breast tissue following Macrolane treatment has led to similar concerns [10,11,15–17]. Because the introduction of Macrolane for breast enhancement was recent, information on whether the presence of Macrolane could obscure the appearance of breast cancer on mammography is scarce. To our knowledge, there is one case report in the published literature that provides some information [15]. A woman with a family history of breast cancer underwent Macrolane injection. Prior to injection, she was noted to have skin tethering; a sign suggestive of breast cancer, but that was not investigated until four

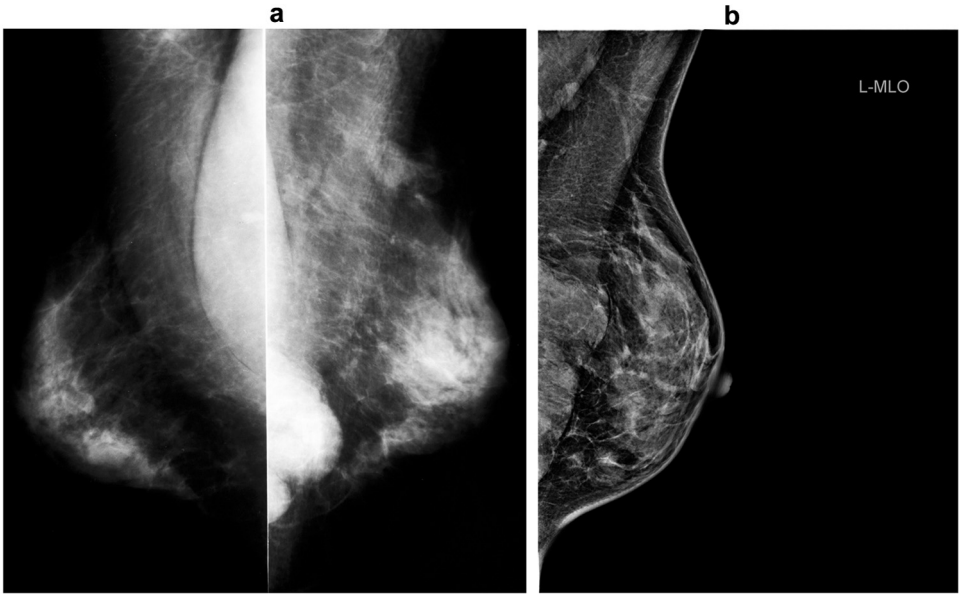

Fig. 4. (a) Sacreen-film mammography (SFM) images: Left: right MLO showing Macrolane under the pectoralis muscle Right: left MLO showing 'imperfect distribution' of Macrolane. (b) Full field digital mammography (FFDM): Left MLO showing Macrolane in the pectoralis.

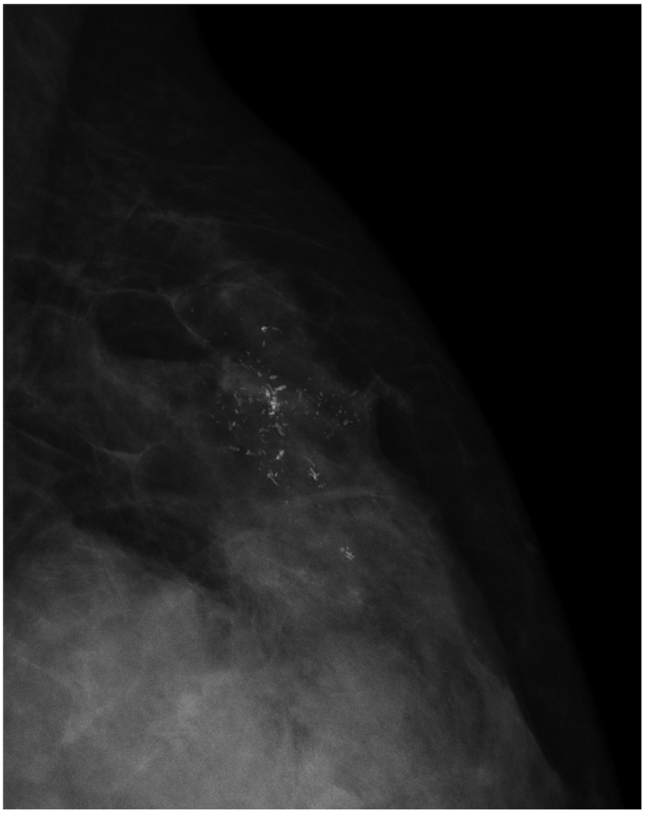

Fig. 5. Visible microcalcifications in a breast treated with Macrolane. The image shows a ductal carcinoma in situ (DCIS), from a study by Yamaguchi et al. (19). The pre-existing micro-calcifications could be seen on the baseline mammogram prior to injection of Macrolane. The DCIS was therefore present but undiagnosed before treatment. Repeat mammography performed at 12 months show the micro-calcifications were clearly visible on the mammogram near the Macrolane.

months after treatment with Macrolane. The mammogram clearly showed a spiculate area of increased density with in-drawing of the skin, as well as multiple cystic opacities. Ultrasound revealed a 1 cm irregular hypoechoic mass consistent with malignancy. Core biopsy of the lesion confirmed lobular carcinoma. In the mammogram provided in the case report, the breast cancer was visible despite the presence of Macrolane.

A particular area of concern is how to distinguish benign microcalcifications from malignant lesions with mammography [10]. However, even in dense breasts, microcalcifications can be seen despite the presence of cysts or other dense tissue or implants such as Macrolane (see Fig. 5). The current gold standard practice is histological confirmation using stereotactic core biopsy regardless of whether Macrolane is present.

2.4. Investigation of suspect lesions with imaging

On mammography, Macrolane can be visualized with a higher density than breast tissue because of its high water content (Figs. 1 a, 4 a and b). It may have the appearance of dense nodules, similar to non-homogeneous glandular tissue. Therefore, breasts treated with Macrolane should be evaluated in a similar manner to mammographically dense breasts, i.e. with additional imaging modalities, typically ultrasound (Fig. 1c). Increases in breast density are known to significantly reduce the ability to visualize cancers on mammography. In a large study involving 3418 asymptomatic women with mammographically dense breasts, the addition of automated breast ultrasound to mammography in women with greater than 50% breast density resulted in an almost three-fold increase in detection

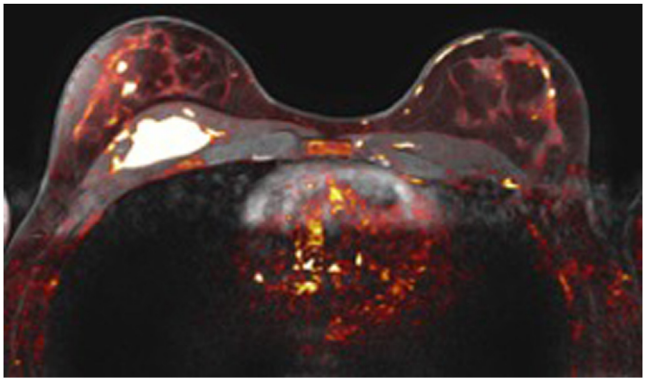

Fig. 6. Macrolane enhanced by image fusion (STIR and BiLateral Imaging in transverse view with SENSE [BLISS]) showing Macrolane (white), blood tissue (red) and vessels (yellow).

of breast cancers using the combined methods compared to mammography alone [12]. Ultrasound (possibly in combination with Doppler and/or contrast enhanced MRI see Fig. 6) may also help to differentiate Macrolane from a solid lesion.

There was consensus amongst participating experts that radiologists currently have the imaging techniques available to assess women treated with Macrolane. However, any recommendations on imaging of women with Macrolane must always be considered within the recognized national and local guidelines.

3. Conclusion

Macrolane has proven to be a challenge for radiologists, with variability in placement, appearance and longevity in the breast. Despite familiarity with the presence of other implants, there is uncertainty amongst radiologists regarding the masking of cancerous lesions and the possibility that diagnosis and treatment may be delayed. Many of the women presenting for breast enhancement are young (aged 20–30 years) and the impact on future mammography remains unknown. This review of imaging should aid radiologists in the selection of the most appropriate modality when imaging women presenting with Macrolane in their breasts, either for routine screening or for symptomatic referral. However, sharing of case reports and further studies are still needed to aid familiarity and increase confidence amongst radiologists.

Conflict of interest

These authors declare that there is no conflict of interest.

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Contributions

GS, KS, MT, KP, AL, PP, EW and CI participated in discussions and proposed the detailed content of the initial draft, which was then developed by the medical writer. All authors reviewed the initial draft and proposed detailed revisions to the content. All authors have approved the final submitted manuscript.

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The role of breast imaging in macrolane injection—A review and report of three cases

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ABSTRACT

The demand for minimally invasive cosmetic procedures is increasing. Injectable hyaluronic acid is an effective and well tolerated procedure that can be used for breast augmentation and provides predictable long-lasting results if administered appropriately in the correct tissue plane. Concerns already exist regarding the effect of Macrolane™ on breast cancer screening, and we raise a new concern about the need for imaging for its safe administration. We present three cases referred to our centre in the last 2 years with complications associated with Macrolane™ injection, possibly from injection into an incorrect tissue plane. Complications included breast pain, haematoma, cellulitis and abscess formation. We suggest that such aesthetic procedures should be carried out under ultrasound guidance to ensure administration into the correct site, potentially avoiding such complications.

1. Introduction

The use of hyaluronic acid in body shaping and volume restoration via minimally invasive techniques has increased the demand for cosmetic procedures [1]. Macrolane™ (Q-Med AB) a new NASHA-based medical implant, consisting of hyaluronic acid, which already exists within the body and thus is not recognized as a foreign substance, was developed and approved in Europe in 2006 [2]. Macrolane™ is intended to last for 12–18 months in the body, depending on the area treated and the volume used. Macrolane™ should be injected anterior to the pectoralis major muscle and posterior to the mammary gland [2].

As a technique for breast augmentation, Macrolane™ is intended to be minimally invasive, and as such can be administered by a clinician under local anaesthetic. The effect of macrolane on breast imaging following injection has been questioned, and is at present unclear [3–5]. However, the role of imaging in the administration of macrolane has not been studied in detail, and the product is licensed for use without imaging support [2]. We present three cases in which complications have occurred following injection of Macrolane™, and discuss whether they could have been prevented with the use of ultrasound image guidance during injection of Macrolane™.

2. Case report

2.1. Case 1

A 38 year old patient underwent bilateral breast augmentation with macrolane injection in November 2008. The initial cosmetic results and patient satisfaction were good. In June 2009 the patient presented with a seven week history of bilaterally painful breasts. Clinical examination revealed smooth lumps in the retroareolar regions of both breasts with no axillary or supraclavicular lymphadenopathy. Bilateral mammograms demonstrated multiple, relatively well defined soft tissue masses in the breast tissue, some appearing to lie within the muscle on the MLO view (Fig. 1). On ultrasound, these were seen to represent multiple collections of complex fluid, lying both within the glandular tissue and the pectoral muscle, measuring up to 5 cm in diameter. The patient was followed up and the symptoms resolved spontaneously.

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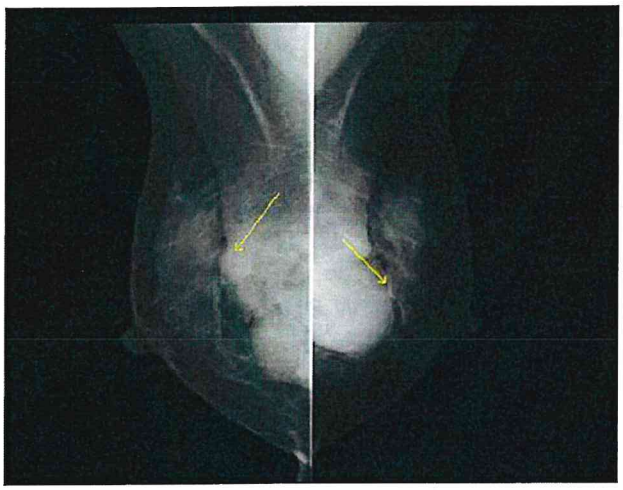

Fig. 1. Bilateral MLO views demonstrate multiple masses within the breast tissue and pectoral muscles.

2.2. Case 2

A 29 year old woman underwent bilateral breast augmentation with macrolane injection in July 2009. Three months after Macrolane™ injection the patient presented with bilateral breast pain and nodularity. Ultrasound and MRI of the breasts revealed multiple complex cystic masses throughout both breasts together with some intramuscular cystic collections of macrolane. There was evidence of delayed rim enhancement around the collections on MRI, presumably secondary to an inflammatory response around the macrolane pockets (Fig. 2). Currently the patient describes symptoms of paraesthesia and breast tightness. The patient has also developed breast asymmetry.

2.3. Case 3

A 30 year old patient presented to the Accident and Emergency department in June 2009 with a painful right breast. She had undergone bilateral breast augmentation with Macrolane™ injection

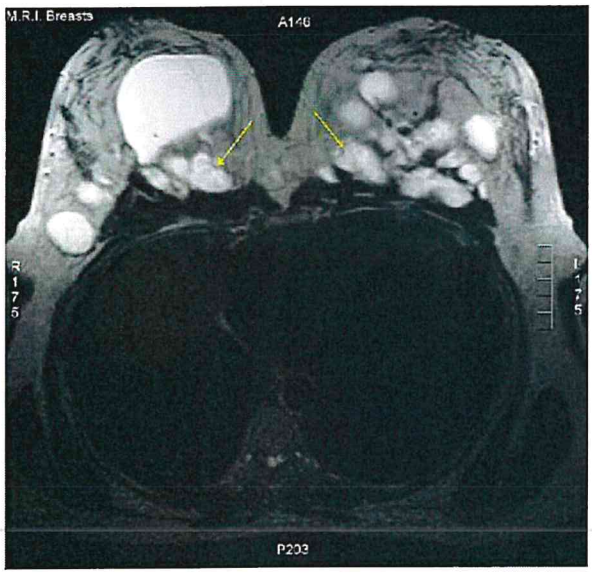

Fig. 2. Axial non contrast T2 weighted MR image demonstrate multiple cystic image within the breast tissue and pectoral muscles.

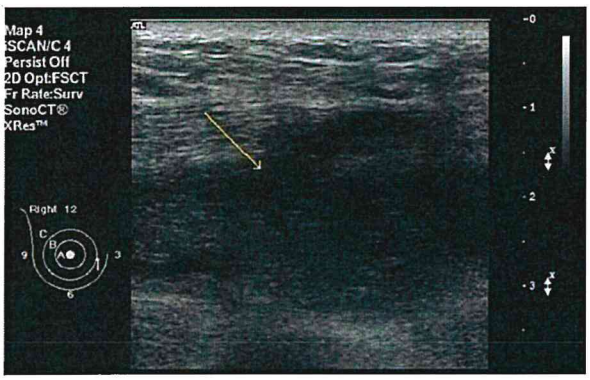

Fig. 3. An ultrasound image demonstrates a complex fluid collection, representing the injected macrolane, with extension of this fluid into the pectoral muscle.

four months previously, followed by a top up injection to correct breast asymmetry. One week following the second injection the patient developed symptoms of tightness and pain in the lateral aspect of the right breast. The patient's symptoms meant that she was unable to raise her arm laterally more than 90°, or pick up even light weights. On clinical examination the right breast was swollen and erythematous, particularly in the lower outer quadrant and her inflammatory markers were elevated, with a CRP of 294. On ultrasound a multiloculated collection was seen in the right pectoral muscle, with evidence of a possible muscle tear and subsequent haematoma (Fig. 3). Intravenous antibiotics were commenced, however her breast pain worsened and the patient underwent surgical incision of a right breast abscess with drainage of 150 ml of purulent bloody discharge. At present, 18 months post surgery the patient has a palpable lump in the right pectoral region and cannot fully raise her right arm above her head.

3. Discussion

Hyaluronic acid, a naturally occurring polysaccharide, is a ubiquitous component of all mammalian connective tissues [6]. In 2008, Macrolane™ VRF was introduced in the UK for use in body shaping and breast volume restoration using hyaluronic acid. Macrolane™ is increasingly being used as a minimally invasive technique for breast augmentation, designed to give the breast a fullness and subtle reshaping by only 1 cup size. The product is intended to be administered between the glandular breast tissue and the fascia of the pectoralis muscle [2]. Studies have shown predictable results with patient and clinician rated improvements lasting up to twelve months [7]. Complications relating to macrolane have been reported. A series of 48 cases describes no major adverse incidents, with 58 of the 69 treatment related minor adverse events described as mild to moderate, and transient in nature, although two patients had to have the implant removed by aspiration [8]. More serious complications as a result of Macrolane™ injection have been reported [4], including at series of 194 women from a single institution, that reported an occurrence of major adverse events of 8.7% including infection, capsular contracture, early resorption and product removal [9].

The three cases described demonstrate a variety of complications—some transient, but others leaving long-term problems. In all three cases the presence of Macrolane™ within an unintended tissue plane – including pectoralis muscle and mammary tissue – is demonstrated on imaging investigations. Without imaging support during the injection procedure, it is difficult for clinicians to confirm the correct placement of the implant. As our cases suggest, injection into an incorrect anatomical structure can result in complications such as breast pain, haematoma, cellulitis, and abscess formation.

A reliable, minimally invasive, non-permanent breast augmentation product remains appealing to patients and clinicians. The role of Macrolane™ in breast enhancement is gaining in popularity, though further research is needed to assess long term efficacy and safety. The role of imaging in the administration of minimally invasive products for breast enhancement, including Macrolane™, needs further investigation. Our experience suggests that ultrasound image guidance should be used whilst injecting Macrolane™ into the sub-mammary space to reduce the incidence of misplacement and the ensuing complications. Furthermore, in agreement with other reports [8] we suggest that macrolane injection is avoided in patients who have a history of malignant, pre-malignant, or even benign breast lesions until further research elucidates the implications for breast imaging.

Conflict of interest

The authors declare no conflict of interest.

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Pictorial Review

The imaging features of MACROLANE™ in breast augmentation

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Macrolane™ is an injectable, biocompatible, soft-tissue filler that has been available in the UK since 2008 and is promoted for use in breast augmentation. There are few data available on the long-term effects of this relatively new product and concerns have been raised about the implications for breast imaging, in particular breast screening. In this context we present a spectrum of imaging appearances and complications encountered to date.

Introduction

Macrolane™ is an injectable, biocompatible soft-tissue filler developed for a cosmetic market with an ever-growing demand for minimally invasive techniques. It was developed by Q-med, a Swedish company renowned for producing similar fillers that are approved by the US Food and Drug Administration (FDA) for facial tissue augmentation.[1] Macrolane was approved in Europe in 2006.[2]

Macrolane has been available in the UK since 2008, and is promoted for use in volume restoration and shaping of soft tissues including the breasts.[3] Breast augmentation is used to increase size, correct deformity and asymmetry, and reconstruct after cancer surgery. Fillers for breast augmentation can be encapsulated (these need surgical implantation) and non-encapsulated (injectable products).

Product information

Macrolane is a gel derived from hyaluronic acid (also known as hyaluronan), a polysaccharide that is present in all mammalian connective tissue. Non-animal origin stabilized hyaluronic acid (NASHA) is naturally degraded and is expected to be resorbed over 12–18 months, hence Macrolane is marketed as a temporary filler.[2]

In 2007 two improved versions of Macrolane with two different volume-restoration factors (VRF) received CE approval in Europe. Macrolane VRF30 is intended for deep subcutaneous injection, whereas Macrolane VRF20 is intended for superficial injection in areas with thin tissue cover such as the hands.[4]

Injection procedure

Macrolane injection for breast augmentation is performed as an outpatient procedure under local anaesthetic. The recommended technique for injection involves either a single-needle pass (single cavity) or multiple passes (multiple cavities) during which up to 100 ml of gel is injected into a potential space between the pectoralis major muscle and the glandular breast tissue. The breast is lifted and the bevel should be held away from the pectoralis muscle, both to minimize injection into the soft tissue. The gel is injected into the areas where volume is desired.[4]

Following injection the breast can be massaged to aid contouring of the gel with the surrounding tissues. The aim is for a 1–1.5 increase in cup size. Top-up injections with

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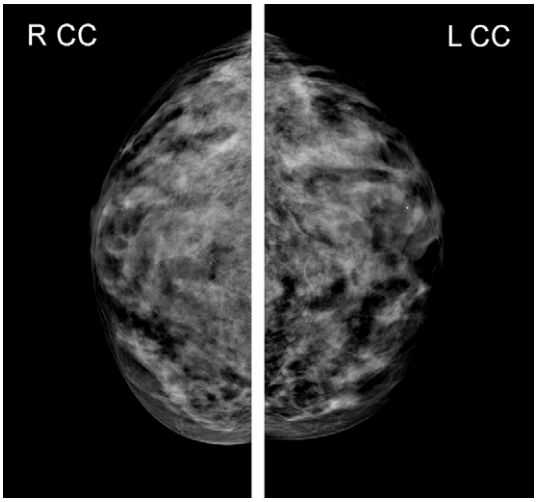

Figure 1 Craniocaudal (CC) view demonstrates a non-specific general increased density in the breast parenchyma in a patient following Macrolane injection.

smaller volumes can be given every 9–12 months if required as augmentation is temporary due to natural resorption of the product.

Advantages

The main advantages to its use include the fact that Macrolane is derived from a naturally occurring substance, therefore, posing a low risk for immunological reactions. It is degraded and resorbed over 12–18 months, which in turn should lower the risk of granuloma formation, whilst at the same time appealing due to its non-permanence.[4] Results are instant without the trauma of surgery under general anaesthetic.

Initial results

The use of Macrolane was initially explored in an ethically approved multicentre pilot study in Sweden. Twenty patients with a mean age of 37 years received an average volume of 97.8 ml injected into each breast. Seventy-five percent reported an improved cosmetic appearance at 6 months. Sixteen patients reported a total of 44 adverse events, the majority (80%) of mild to moderate intensity. The commonest adverse events were pain and capsular formation/contraction.[4]

In another study in Japan 1100 patients were treated with a different kind of hyaluronic acid, Restylane SubQ^{TM}. An average of 40 ml was injected per breast. Only three complications were reported: two cases of infection and one patient presenting with a lump at the injection site. Long-term outcomes and patient satisfaction were not discussed.[5,6]

There is little further published scientific data evaluating the safety and efficacy of Macrolane, and in particular, no long-term follow-up results are yet available.

Concerns

Concerns have been raised in the literature that the long-term safety of this new product has not been established

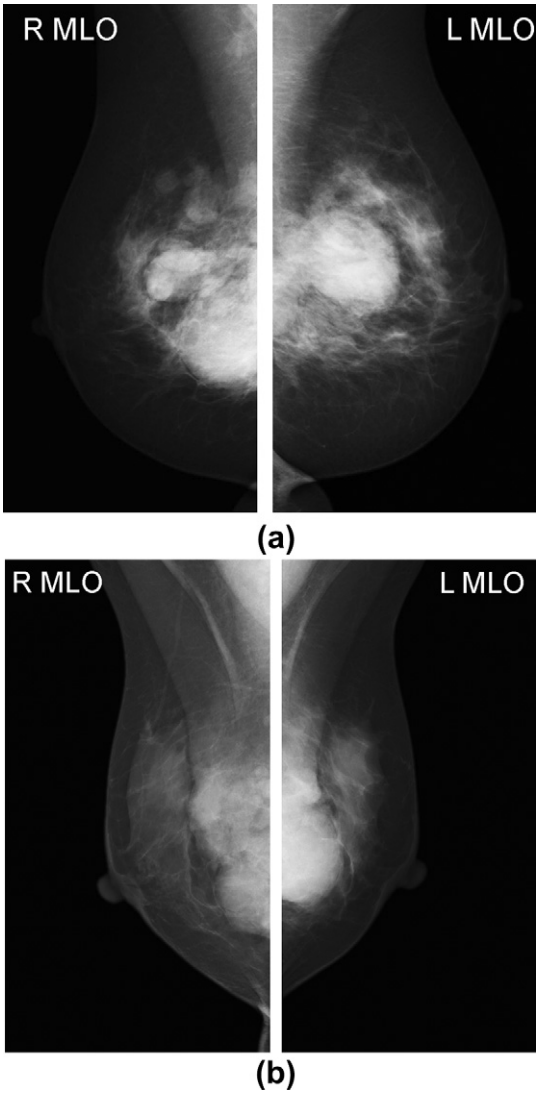

Figure 2 (a–b) On medio-lateral oblique (MLO) views of two different patients Macrolane is seen as a mixture of general increased density, as well as more focal lesions, both within the parenchymal breast tissue and the pectoralis muscle.

and that the implications for breast imaging, in particular breast cancer screening, are not yet known.[2] Available research to date demonstrates only minimal degradation of Macrolane, with radiological evidence of persistence within the breast up to 24 months post-procedure. Unlike small volumes of Macrolane used in the face, larger volumes may stay in the breast for an indeterminate time.

The current technique of Macrolane injection, even with a single pass, allows migration of the product following the path of least resistance, which can result in irregularly shaped deposits. Initial studies showed Macrolane deposits in the breast, pectoralis muscle, and also below the muscle.[2] In local experience the latter two have been associated with pain, with one patient being followed up for 2 years due to intractable pain in the chest wall and arm following injection into the pectoralis muscle. The long-term effect of the implant being in an undesired location is unknown.

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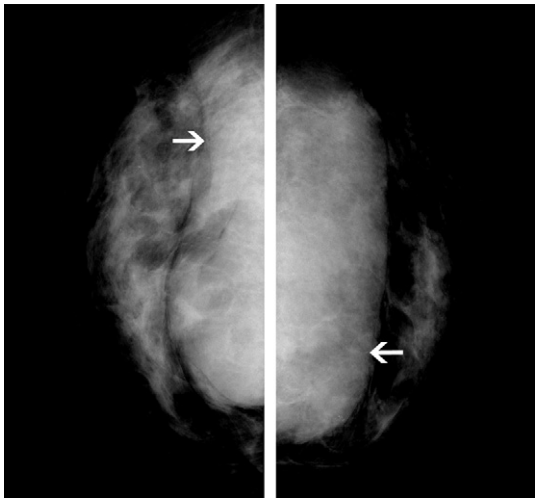

Figure 3 Macrolane in pectoralis causing a bulging density in the muscle (arrows).

Since its introduction a number of complications have been documented following Macrolane injection for breast augmentation. In the authors' local practice similar problems have been encountered. Patients have presented with breast pain, superficial infection, and abscess formation. On clinical examination generalized breast hardness and nodularity has been reported, in addition to changes in the shape/contour of the breast and discrete palpable lumps.

In patients presenting with breast lumps the clinical and associated imaging findings can pose practical difficulties in differentiating Macrolane deposits from more sinister disease, necessitating additional imaging and even tissue sampling to complete triple assessment. Surgical exploration of such nodules demonstrated multiple Macrolane deposits surrounded by individual fibrous capsules. Histology revealed a foreign-body response in the adjacent connective tissue.[3]

Capsular formation poses a further specific problem in its tendency to cause calcification, which has obvious implications for imaging in particular in relation to breast screening.[3] In local experience two patients underwent stereotactic biopsy of microcalcification seen on mammography following Macrolane injection. The histology was, in these cases, non-specific and felt to be unrelated to the Macrolane. The association between injection and eventual microcalcification is as yet unclear. Perhaps most worrying is the scientific evidence that increased synthesis of hyaluronic acid is associated with malignant progression of breast cancer — hyaluronic acid is upregulated and plays a major role in cancer cell behaviour. Although it is not thought be a trigger for breast cancer, it may play a pivotal role in its progression.[2,7]

Imaging

To date there is limited published information about the imaging appearances of Macrolane in the breast. In a pilot study 19 patients underwent bilateral breast augmentation with Macrolane and were followed up with a combination of mammography (if aged 35 years and over), ultrasound, and, in a subgroup, MRI up to 24 months post-procedure.[2] The manufacturer states that further studies are

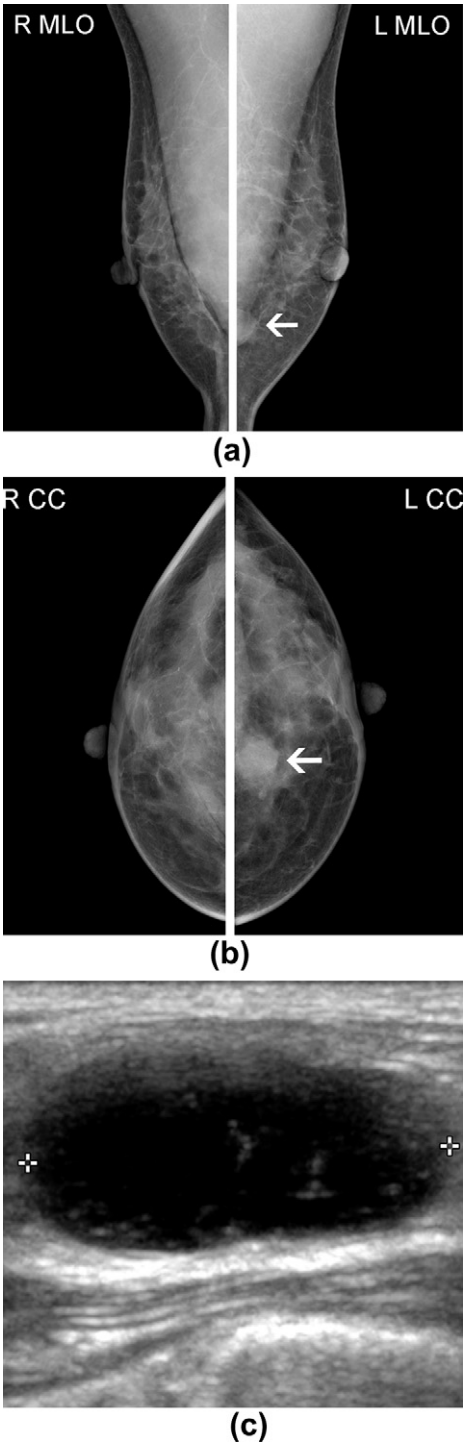

Figure 4 (a) MLO and (b) CC views of the same patient demonstrate increased density within the pectoralis muscles with slight bulging on the left and a more focal ill-defined lesion (arrow) within the left breast. (c) The corresponding ultrasound image of the focal lesion is largely anechoic with some internal echoes. Macrolane deposits were also seen within the pectoralis muscle on ultrasound (see Fig 6).

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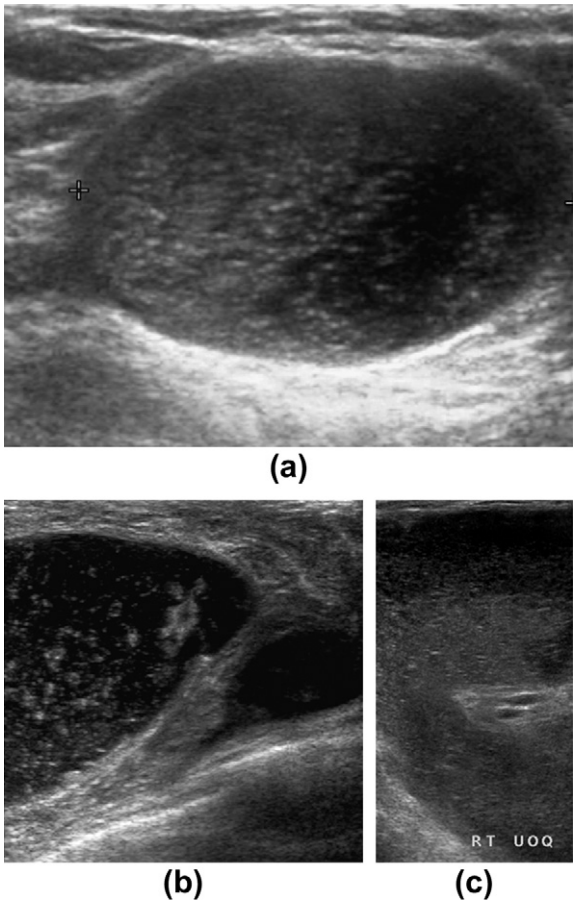

Figure 5 (a–b) "Sparkly lake" sign — largely anechoic areas containing multiple internal echoes of varying size and echogenicity are typical of uncomplicated Macrolane collections on ultrasound. This has to be differentiated from more sinister pathology such as an abscess, as demonstrated in (c).

underway to evaluate the appearances and impact of Macrolane injection on breast imaging.[8]

Mammography

Macrolane leads to increased density of the breast parenchyma on mammography, which may be generalized or appear as multiple, discrete, hyperdense lesions, the latter being the appearance most commonly encountered in our practice. These lesions are denser than simple cysts and benign solid lesions, such as fibroadenomas, although the overall increased density with Macrolane is less than with silicone implants (Fig 1).

In local experience well-circumscribed dense lesions were seen in 14/19 patients and involvement of the pectoralis muscle was seen in 5/19 (Fig 2). When Macrolane is present in the pectoralis muscle it can cause a confluent density visualized on both the oblique and the craniocaudal views, giving a hyperdense bulging convexity to the muscle (Fig 3).

The presence of Macrolane reduces the sensitivity of mammography and creates false positives (Fig 4). The manufacturers suggest that ultrasound can be used as a complementary examination in cases where mammography is difficult to interpret due to the presence of Macrolane in the breast.[8]

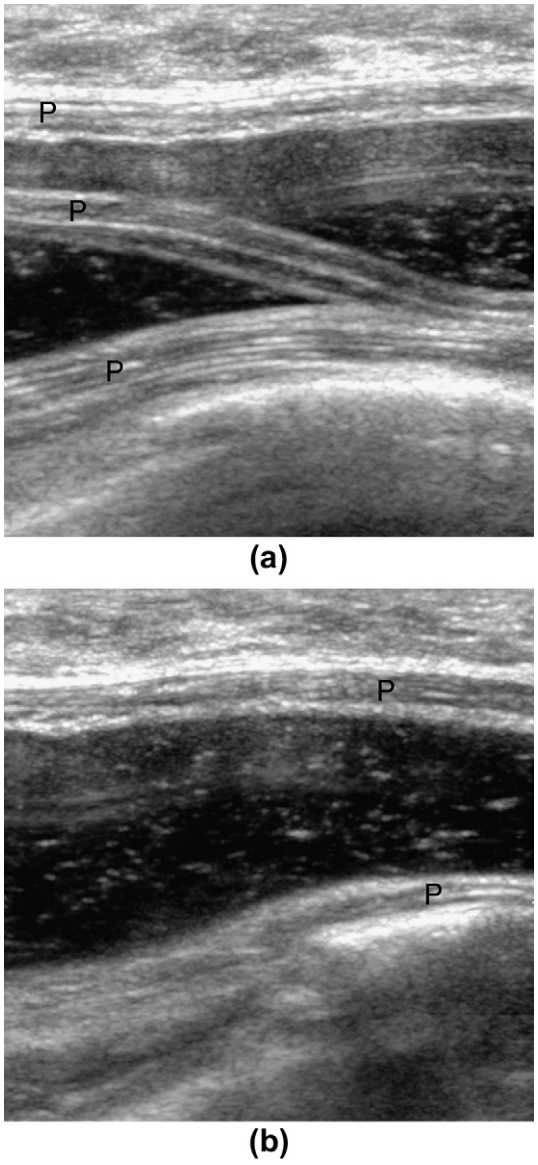

Figure 6 (a–b) Macrolane collections demonstrating the typical "sparkly lake" appearance are seen within the pectoralis muscle (P).

Ultrasound

On ultrasound Macrolane is seen as multiple collections that are largely anechoic but demonstrate internal echoes, which can vary in size and echogenicity; this appearance has been described in our institution as "the sparkly lake sign" (Fig 5).

These collections can be well defined or dispersed within the glandular tissue, sometimes with multiple communicating channels and often within the pectoralis muscle (Fig 6). Internal echoes and interconnecting channels help differentiate these from simple cysts (Fig 7). The location of Macrolane deposits is generally readily appreciated on

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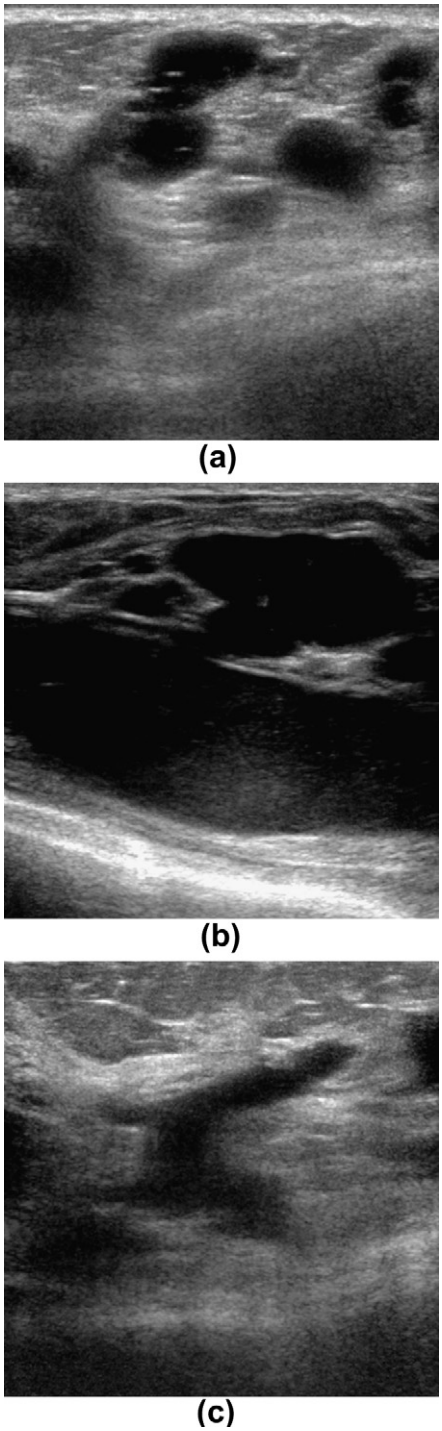

Figure 7 (a) Multiple small collections of Macrolane are seen within the breast parenchyma. (b–c) Intercommunicating channels are seen between Macrolane collections throughout the parenchyma of the whole breast and in the pectoralis muscle.

imaging; in particular, ultrasound has proved a very useful tool in this regard.

Our experience shows that over time some of the collections (in 4/19 patients) show a more solid appearance, such patients going on to have a core biopsy of the lesions under ultrasound guidance. Histology revealed the presence of Macrolane, fibrous tissue, and in one case a foreign-body reaction. No suspicious features were identified.

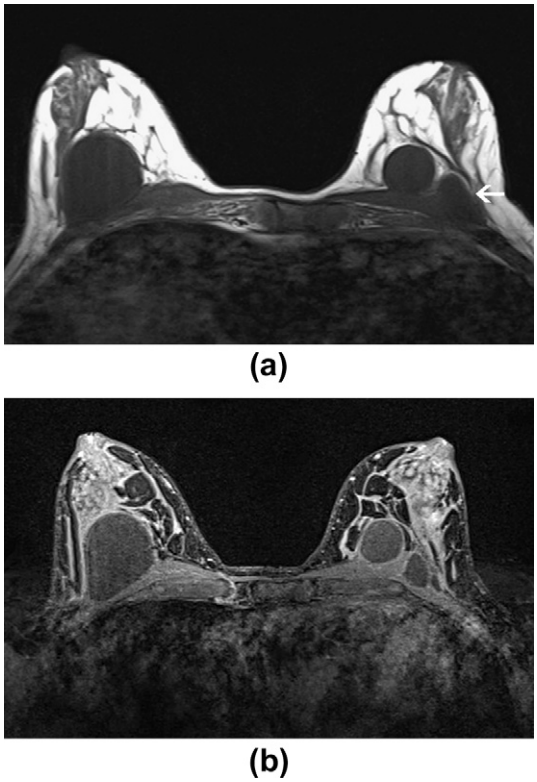

Figure 8 (a) Axial, T1-weighted and (b) T1, fat-saturated post-gadolinium enhancement sequences demonstrate larger collections of Macrolane within the breast parenchyma and pectoralis muscle (arrow). Deposits are low signal intensity on T1 with minimal rim enhancement post contrast medium administration.

Apart from its main role as diagnostic complement to clinical evaluation and mammography, ultrasound has been used locally to guide drainage of Macrolane collections as per patient request, mainly for complaints relating to palpable lumps, hardness of the breasts, and pain following Macrolane injection. Patients have opted for eventual silicone implants as regular Macrolane top-ups were proving to be both expensive and inconvenient.

In local practice aspiration of Macrolane deposits has proved a lengthy procedure involving multiple needle passes given the presence of multiple collections. Due to the crystalline nature of the fluid Macrolane aspiration is often unsuccessful and yields only a small amount of material, leaving most of the Macrolane *in situ*. The residual clinical abnormality causes ongoing patient anxiety.

Breast ultrasound is furthermore often requested to assess the residual volume of Macrolane prior to further top up injections.

MRI

MRI has been used in a few instances locally as a problem-solving tool when conventional imaging is indeterminate; in particular, to distinguish Macrolane deposits from more

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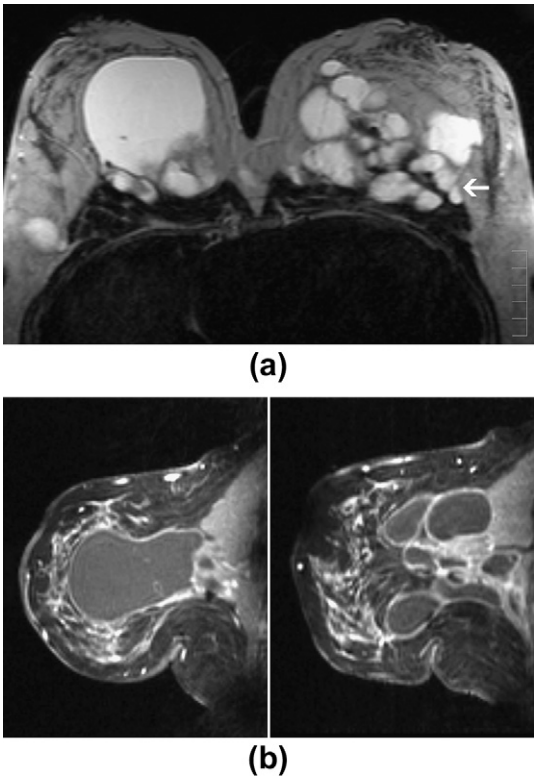

Figure 9 (a) Axial, T2-weighted and (b) sagittal, T1-weighted, fat-saturated, post-gadolinium sequences demonstrate a large collection of Macrolane within the parenchyma on the right with multiple smaller collections in the left parenchyma and pectoralis muscle bilaterally. Deposits are high signal intensity on T2, low signal intensity on T1 and demonstrate rim enhancement post contrast medium administration.

sinister pathology. Although it is not suggested that contrast medium should be administered routinely, contrast-enhanced MRI has been performed to look for the presence of any suspicious enhancing features in order to avoid unnecessary sampling of deposits. MRI has also been utilized in the evaluation of ongoing intractable pain in the chest and breast 6 months following Macrolane injection.

MRI of the breast with Macrolane implants should be performed at day 6–14 of the menstrual cycle (as in screening breast MRI) as the majority of the women who undergo Macrolane injection are young. This prevents false positives from enhancement of the normal breast parenchyma.

In pilot studies NASHA gel remained visible on MRI at 24 months, showing irregular and asymmetrical distribution in the breasts.[2,4]

Macrolane appears as areas of low T1/high T2 signal, similar to complex cysts. These are generally well circumscribed within the glandular tissue or involving the pectoralis muscle. Experience to date suggests that rim enhancement of Macrolane deposits may occur normally following the use of intravenous contrast medium[9]. This may be secondary to local tissue reaction (as indeed demonstrated histologically both locally and elsewhere[3]). The significance of rim enhancement is uncertain and the clinical context is necessary to differentiate from infection (Figs 8 and 9).

Conclusion

Macrolane is widely advertised for its cosmetic use in breast augmentation. It is a relatively new product, on the European market since 2006 and in the UK since 2008, and long-term effects have not yet been established. Main advantages include its natural origin, instant results without surgery, and non-permanence due to natural resorption.

Although marketed as a temporary filler, initial studies showed that Macrolane was still visible on imaging at 24 months. The clinical and radiological sequelae, therefore, have to be considered for an as yet unknown length of time.

Concerns have been raised about the implications of Macrolane injection on breast imaging and in particular breast screening. On mammography Macrolane obscures the normal breast tissue to a varying extent and complicates interpretation of images, often resulting in further imaging.

Palpable lumps have been attributed to capsular contracture related to Macrolane deposits. These may be difficult to distinguish from sinister pathology both clinically and radiologically and will inevitably result in further imaging and even tissue sampling. A major concern is that patients may attribute breast lumps to Macrolane and present late with more sinister pathology. Alternatively, if the breasts are hard and lumpy following Macrolane then patients may be unable to palpate smaller more sinister lumps.

The tendency for calcification within capsular contractures poses a further particular problem in breast screening.[3] A possible relationship between Macrolane and microcalcifications on mammography remains indeterminate pending further clinical and radiological experience.

Larger volumes of injection in the breast may allow migration of Macrolane from its desired location in the potential space between the glandular breast tissue and the pectoralis muscle. In our patient group Macrolane deposits were often seen within the pectoralis muscle and have been associated with pain.

The spectrum of imaging appearances encountered to date provides a basis for the radiological evaluation of patients following Macrolane injection, whether for the purposes of routine screening or complications following injection. Clinical and radiological follow-up will provide further information on the long-term radiological evolution of Macrolane in the breast.

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