aesthetic medicine

Case Report

Insidious diagnosis of breast cancer in patient with previous MacrolaneTM breast infiltration: a case-report

Ugo Redi MD, Gianmarco Turriziani MD, Federico Lo Torto MD, Giovanni Marruzzo MD, Jacopo Nanni MD, Marco Marcasciano MD, Diego Ribuffo FP

Department of Plastic, Reconstructive and Aesthetic Surgery, Sapienza University of Rome, Viale del Policlinico 155 - Roma

Running head: Breast cancer Macrolane filler

Abstract

Breast augmentation is one of the most performed aesthetic surgery. In addition to the silicone breast implants, hyaluronic acid base fillers represent a non-surgical alternative. There are different types of hyaluronic acid for this purpose, including MacrolaneTM. In addition to the classic complications associated with the mammary injection of these fillers, Macrolane may cause a well-known radiological ambiguity potentially leading to a delay in the diagnosis of an underlying breast cancer.

The patient underwent breast augmentation with hyaluronic acid and after several years from the procedure she noted the appearance of subcutaneous nodules and discontinuous mastodynia, attributed to previous Macrolane infiltrations: unfortunately the radiological images did not immediately show the underlying contextual cancer of the right breast.

Patient underwent therapeutic right mastectomy and prophylactic left mastectomy, because of the presence of BRCA1 mutation. Simultaneously we performed an immediate reconstruction with mammary implants and biological meshes. No complications arose in the follow up.

Several authors have already carried out studies on Macrolane focusing on its interference and delay in the diagnosis of malignant breast diseases. At present there is only one other case in literature reporting on a patient diagnosed with physical and instrumental examinations and delaying the diagnosis. We believe that the use of hyaluronic acid (Macrolane) fillers for breast augmentation should be avoided. In view of the complexity of these cases, a multidisciplinary approach is always advisable: we believe that a continuous dialogue between the Plastic surgeon, the Breast-dedicated Radiologist and the Oncologist is pivotal.

Keywords

Macrolane, Breast Cancer, Hyaluronic Acid, Ductal Carcinoma, Breast Reconstruction

Received for publication August 30, 2020; accepted September 21, 2020 - © Salus Internazionale ECM srl - Provider ECM no 763

Correspondence

Gianmarco Turriziani, MD

Address: Via Piede la Valle 13, Broccostella, 03030 (Italy)
Phone: +39 3204922732
E-mail: gianmarco.turriziani@gmail.com

Introduction

The surgical procedures of breast augmentation and the use of fillers for cosmetic minimally-invasive procedures are among the main treatments increasingly required, according to the 2018 National Plastic Surgery statistics. Macrolane is a highly cross-linked, stabilized, non-animal and biodegradable hyaluronic acid-based gel (NASHA technology). After the European approval for its use in breast augmentation procedures in 2008, Macrolane was considered a valid non-invasive alternative to prosthesis mastoplasty[1].
Following the growing evidence of radiological ambiguity associated with its use as a breast filler[2-5], Macrolane was banned for this indication in 2012.
Currently in the literature there is only one case of breast cancer arising after mastoplasty with Macrolane, which masked an underlying cancer, interfering with physical and instrumental examinations and delaying the diagnosis[6].

We report a new case of breast cancer in a patient who had previously experienced bilateral mammary Macrolane injections, causing difficulties in diagnosis.

Case Report

A 54-year-old woman, non-smoker, with negative pharmacological and remote pathological anamnesis, but with family history of breast and pancreatic cancer, underwent aesthetic bilateral breast augmentation with hyaluronic acid (MacrolaneTM) in 2008 in another facility. The patient reported slow onset of discomfort and itching, followed by progressive appearance of subcutaneous nodules and discontinuous mastodynia. For these reasons in 2014 she was examined by her General Practitioner, who prescribed further imaging tests (two breast ultrasounds, a mammogram and an MRI between 2014 and 2018).

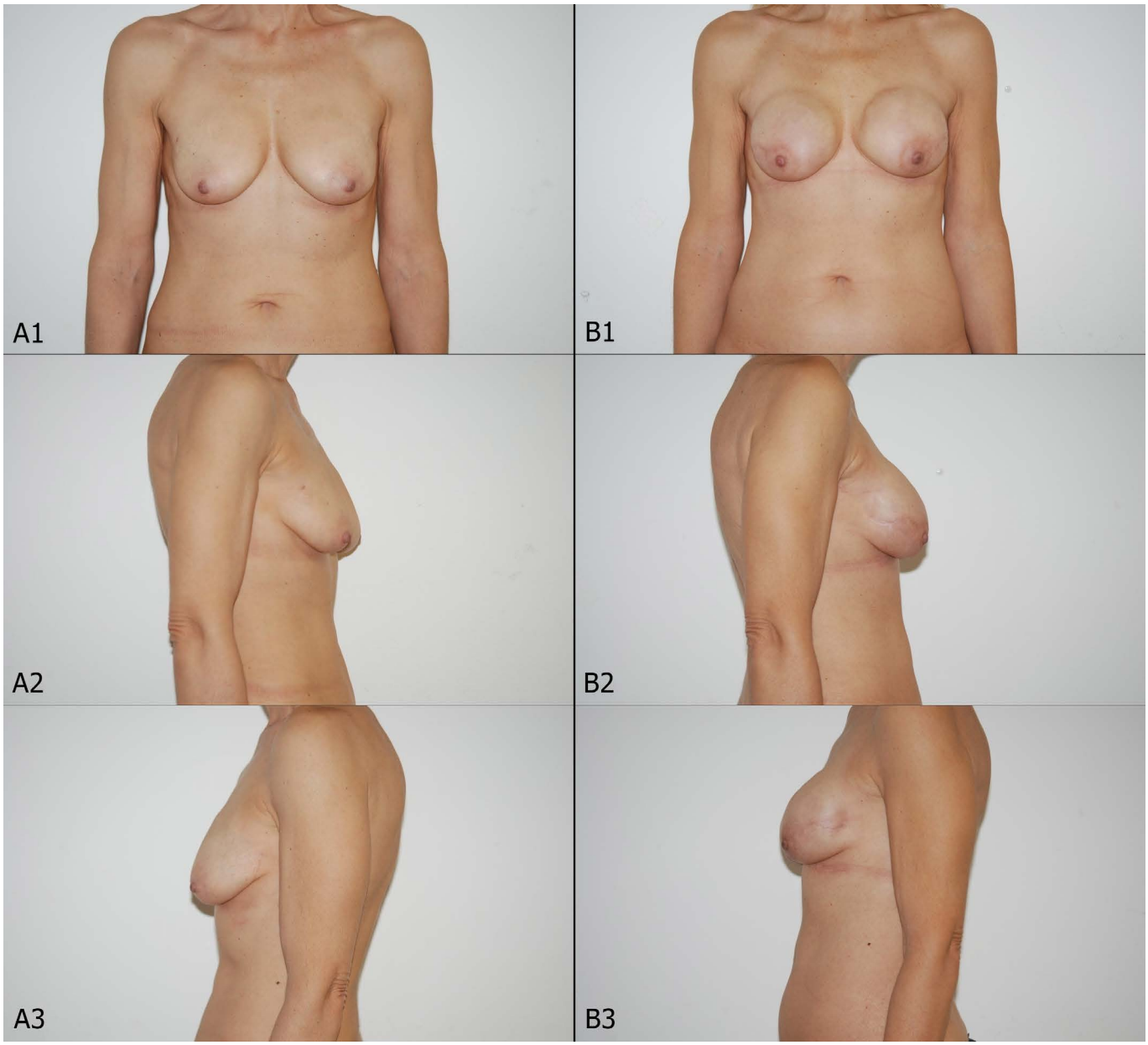

Figure 1 *- Preoperative photos (A1,2,3) and postoperative photos at five months (B1,2,3).*

These examinations showed an ambiguous and infrequent radiological imaging, so a more in-depth evaluation was required to rule out the presence of concurrent malignancy signs.
Therefore, with the deterioration of the local clinical and aesthetic conditions, the patient was referred to our Department. The clinical examination showed a slight mammary asymmetry with irregularity of the cutaneous surface and the presence of superficial and deep bilateral breast nodules (*Figure 1 - A1, A2, A3*).
The patient was unable to give us information about the quantities or the method of injection of Macrolane. MRI showed the presence of multiple adjacent and partially confluent areas with fluid contents; mammary bodies with a prevalence of fibro-glandular tissue; no clear focal lesions or areas with pathological enhancement after contrast administration. Consequently, ultrasound scan and mammogram were integrated.
Ultrasound confirmed the presence of fibro-glandular breast tissue with medium-high density and the presence of numerous non echogenic formations with regular contours bilaterally; no signs of periareolar ductal ectasia or suspicious lymph nodes in the axillary cavities, but some lymph-nodes with a non-specific reactive aspect. Mammogram (*Figure 2*) showed widespread signs of homogeneous thickening with unstructured fibrous opacities and numerous nodular opacities with poorly delimited margins. Moreover, it showed the presence of numerous micro-calcifications grouped in an area of about 20 mm in the upper-outer right quadrant, not reported in the last mammogram. A mammotome biopsy was performed in this area: the histological examination showed the presence of diffuse foci of intermediate-high grade ductal carcinoma in situ and a focus of infiltrating ductal carcinoma.
In addition, due to the positive family history for breast cancer in two first- degree relatives, mutation research for the BRCA gene was performed: BRCA1 gene was mutated. The case was subsequently discussed by a dedicated multidisciplinary team, which focused on the difficulty in interpreting the mammograms due to the presence of dense breast tissue.
For this reason, because of her family history and the presence of mutated BRCA1, the patient underwent bilateral nipple-sparing subcutaneous mastectomy, with an S-italic approach and contextual sentinel lymph-node biopsy in the right axilla.
After removal of the glands, the remaining hyaluronic acid cysts were identified in the subcutaneous tissue, on the fascia and in the pre-insertional anterolateral region of the Pectoralis Major muscle and removed (*Figure 3*). The patient underwent a pre-pectoral breast reconstruction with bilateral silicone implants (MENTOR® - Smooth Round Moderate Plus Profile Gel Breast Implant Cohesive I, n° 350-2501 BC: volume 250 cc, diameter 11.3 cm, projection 3.4 cm) with the use of biological mesh (Braxon® ADM) (*Figure 1 - B1, B2, B3*).
Definitive histological examination showed the presence of fibrocystic mastopathy with micropapillary apocrine metaplasia, on the left, and the presence of numerous foci of ductal carcinoma in situ (DCIS), with intermediate nuclear grade, necrosis and microcalcifications, on the right (*Figure 4 - A*). Sentinel lymph-node was free from infiltration [TNM-AJCC 2017 classification: pTis pN0 (sn) (0/4)]. The hyaluronic acid nodules appeared as aggregates of amorphous and weakly basophilic material (*Figure 4 - B, C*).

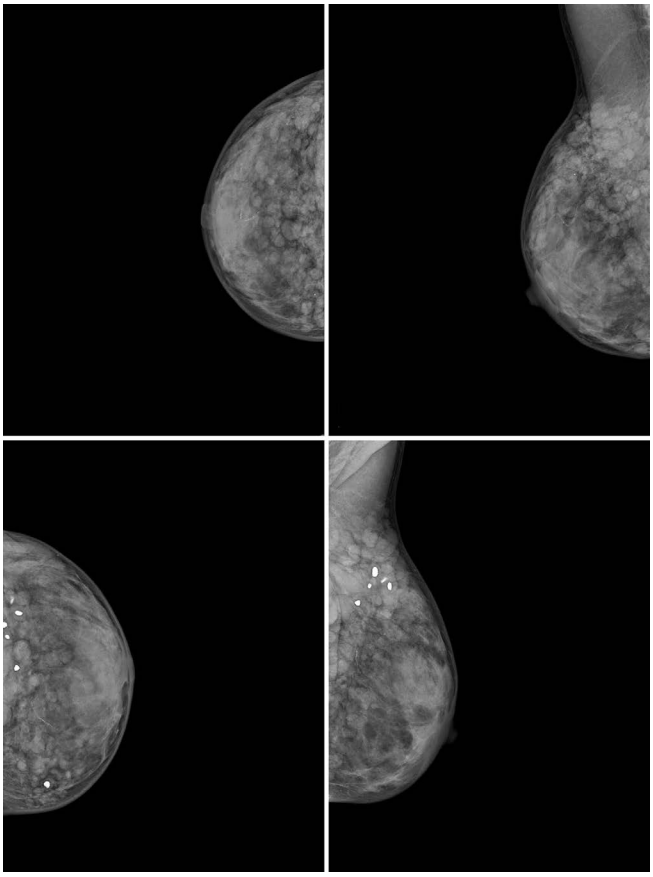

Figure 2 *- Bilateral mammogram.*

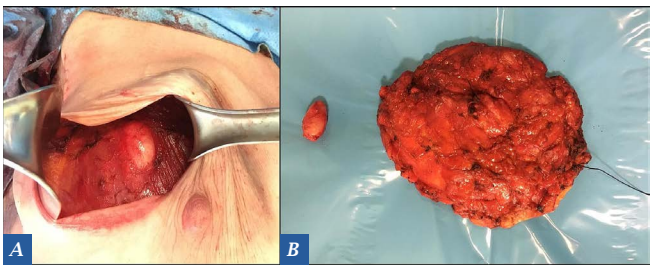

Figure 3 *- Intraoperative time: hyaluronic acid cyst between the fibers of the right Pectoralis Major Muscle (A); right mammary gland with multiple hyaluronic acid cysts and the excised cyst on the left (B).*

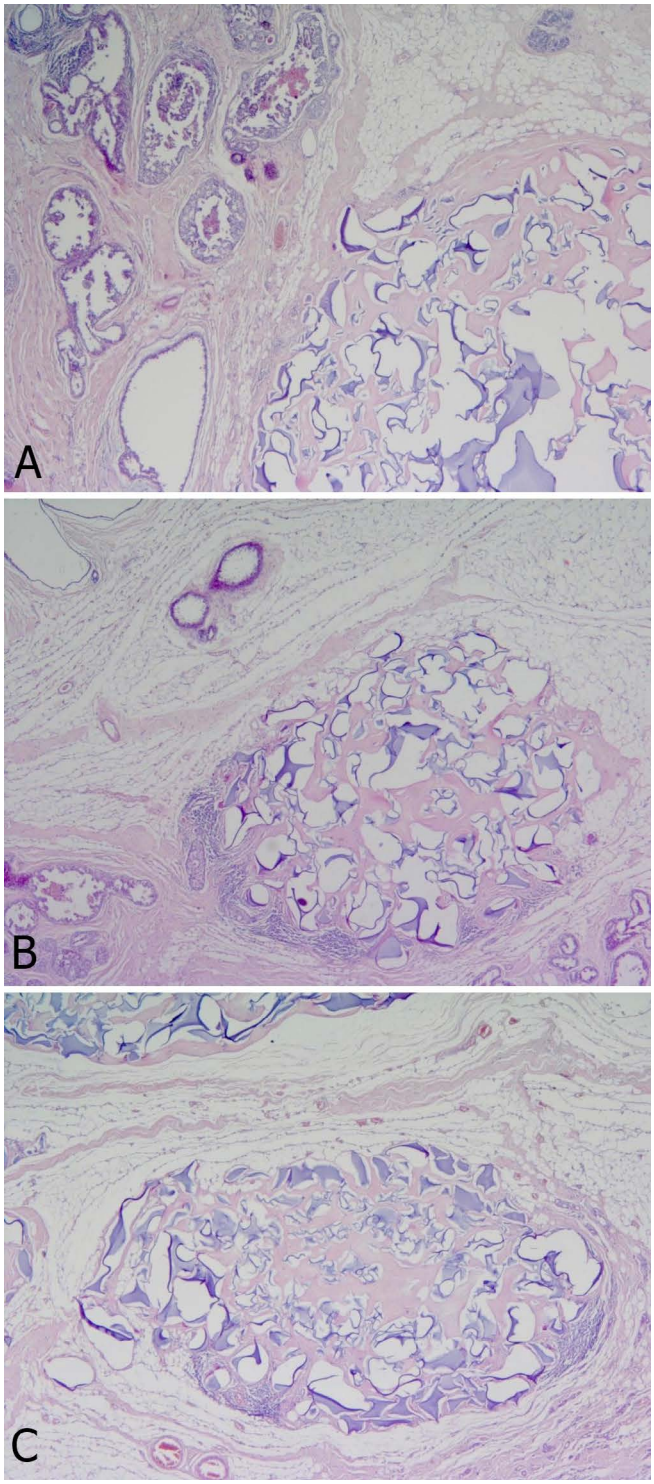

Figure 4 *- Histological slides: foci of ductal carcinoma in situ on the left and hyaluronic acid cyst on the right (A); hyaluronic acid cysts (B-C).*

Discussion

According to the 2018 National Plastic Surgery statistics, the surgical procedures of breast augmentation and the use of fillers for cosmetic minimally-invasive procedures are among the main treatments increasingly required.
Macrolane is a highly cross-linked, stabilized, non-animal and biodegradable hyaluronic acid-based gel, distributed by the Swedish Q-Med company. Since 2006 Macrolane has been available on the European market, as a resorbable filler for all body areas except for face and breast. In 2008 the European Community approved the use of Macrolane in breast augmentation procedures. Macrolane was considered a valid non-invasive alternative to prosthesis mastoplasty since it is resorbable and with the possibility of retreatment, its injection is fast, does not require general anesthesia and leaves no visible scars[1]. Furthermore, the allergic reactions and infections rates are lower compared to other breast augmentation techniques[7-8].
Following the growing evidence of radiological ambiguity associated with the use of Macrolane as a breast filler and after France banned this last indication in 2011[9], Q-med decided to temporarily suspend this indication in 2012. In the same year, this use was also prohibited in Italy[10].
Macrolane infiltrations can lead to various complications such as infections[11]: treatment involves the use of antibiotics and the possibility of evacuating collections of pus and hyaluronic acid. Despite the reabsorption capacity of Macrolane, its degradation mechanism and the consequences of repeated infiltration remain largely unknown[9]. The average reabsorption time is of about 18 months[12-17], but in the literature there are cases of persistence of Macrolane even beyond 24 months[2] and up to 4 years[18]. On the other hand, there are reports on cases of early Macrolane degradation before 6-12 months after infiltration[11]: therefore, aesthetic results are difficult to predict[3]. A single product infiltration is associated with longer degradation times: this is why it was recommended to inject Macrolane as a single implant below the mammary gland[11,19]. A single infiltration can also prevent other complications: firm breast and visible nodules, dislocation, radiological ambiguity. The superficial nodules can be treated with mechanical compression, whereas the deepest nodularities can be aspirated. In refractory or product dislocation cases, targeted injections of hyaluronidase are a good option[20].
The progressive limitation of the use of Macrolane for breast augmentation is a consequence of its interference with radiological examinations[2-6]. Macrolane is 98% water so its imaging characteristics will be similar to water. When there are multiple deposits in the breast, it is difficult to distinguish them from the glandular tissue. In addition, as Macrolane is a product not yet familiar to radiologists[21], it can mask breast conditions[19].
Sometimes the radiological images show solidified nodules and calcifications, so they can mimic breast cancer[6,9]: in these cases a biopsy must exclude malignant lesions[2,22-25]. In their report, Becchere et al. showed how Macrolane masked images of hypoechogenic lesions previously visualized in the preoperative time[26].
Finally, some authors hypothesize a possible increase in the risk of breast cancer following infiltration of hyaluronic acid-based fillers in the breast.
The infiltration procedure is advocated to be traumatic leading to inflammation of the breast tissue[3,5]. Moreover, hyaluronic acid has entered the debate as in some cancer patients there are increased levels of hyaluronic acid: currently, there are no data in the literature that correlate hyaluronic acid to the onset of cancer, nor data that correlate high levels of hyaluronic acid to a worse prognosis in cancer patients. The expression of

high levels of hyaluronic acid could be interpreted as an epiphenomenon, and therefore not the cause, but a manifestation of neoplastic pathology[27].
The use of Macrolane in breast augmentation has been associated with various complications, not related to the product safety or quality. Many authors have highlighted radiological ambiguities in different imaging tests, particularly in mammography. Many authors have carried out studies on this product and on its interference and delay in the diagnosis of malignant breast diseases[2,3,5,6,8,9,20,22,23,27-30]. After an accurate search in the online databases and literature, there is only one case reporting on a patient with breast cancer arising after mammoplasty with Macrolane, which masked an underlying cancer, interfering with physical and instrumental examinations and delaying the diagnosis[6].
As in the case described above so we found the same difficulties, even during the surgery time. Multiple evidences demonstrate that Macrolane remains in place for longer periods than those described in the literature, therefore its mechanism of degradation and reabsorption time remains unpredictable. Due to the clinical, radiological and therapeutic difficulties encountered in the management of patients with previous Macrolane breast infiltration, at present we believe that the use of hyaluronic acid (Macrolane) fillers for breast augmentation should be avoided. Furthermore, it is advisable to perform a complete and correct clinical and instrumental evaluation before any type of breast augmentation procedure, in order to exclude any underlying mammary malignancy: for this reason, a multidisciplinary approach through the Plastic surgeon, the Breast-dedicated Radiologist and the Oncologist is always advisable.

Acknowledgments

- Conflict of interest: the authors declare that they have no conflicts of interest to disclose.
- Statement of human and animal rights: this article does not contain ant studies with human participants or animals performed by any of the authors.
- Informed consent: Informed consent was obtained from all individual participants enrolled in the study.

Conflict of interest

The Authors declare that they have no conflict of interest.

REFERENCES

1. Yamaguchi S, Nagumo Y, Niwa K. Efficacy and safety of Macrolane™ for breast enhancement: A 12-month follow-up study in Asian women. *J Plast Surg Hand Surg.* 2013; 47(3):191-195.
2. Pienaar WE, McWilliams S, Wilding LJ, Perera IT. The imaging features of Macrolane in breast augmentation. *Clin Radiol.* 2011; 66(10):977-83.
3. Chaput B, Chavoin JP, Crouzet C, Grolleau JL, Garrido I. Macrolane is no longer allowed in aesthetic breast augmentation in France. Will this decision extend to the rest of the world? *J Plast Reconstr Aesthet Surg.* 2012; 65(4):527-528; discussion 528–529.
4. Goisis M. Macrolane™ complications after breast augmentation: treatment and prevention. *Eur J Plast Surg.* 2011; 35(4):684-686.
5. Chaput B, De Bonnecaze G, Chavoin JP, Gangloff D, Garrido I. France prohibits the use of Macrolane in aesthetic breast augmentation for reasons similar to criticisms of autologous fat grafting in the breast. *Aesthet Plast Surg.* 2016; 36(4):1000–1001.
6. Crawford R, Shrotria S. Macrolane injections for breast enhancement in undiagnosed breast malignancy: a case report. *J Plast Reconstr Aesthet Surg.* 2011; 64:1682–1683.
7. Inglefield C. Early clinical experience of hyaluronic acid gel for breast enhancement. *J Plast Reconstr Aesthet Surg.* 2011; 64(6):722–729.
8. Van der Lei B. Macrolane: a safe alternative for breast augmentation? *J Plast Reconstr Aesthet Surg.* 2011; 64(6):729–730.
9. Chaput B, De Bonnecaze G, Tristant H, Garrido I, Grolleau JL, Chavoin JP. Macrolane, a too premature indication in breast augmentation. Focusing on current knowledge of the product. *Ann Chir Plast Esthet.* 2011; 56:171-9.
10. Q-Med. Q-Med discontinues the Breast Indication for Macrolane>Galderma>Press Releases Galderma UPPSALA 2012; Sweden: Q-Med.
11. Ishii H, Sakata K. Complications and management of breast enhancement using hyaluronic acid. *Plast Surg (Oakv).* 2014; 22(3):171–174.
12. Buck DW, Alam M, Kim JY. Injectable fillers for facial rejuvenation: a review. *J Plast Reconstr Aesthet Surg.* 2009; 62)1):11–8.
13. Heden P, Sellman G, von Wachenfeldt M, Olenius M, Fagrell D. Body shaping and volume restoration: The role of hyaluronic acid. *Aesthetic Plast Surg.* 2009; 33(3):274–82.
14. Heden P, Olenius M, Tengvar M. Macrolane for breast enhancement: 12-month follow-up. *Plast Reconstr Surg.* 2011; 127(2):850–860.
15. Kanchwala SK, Holloway L, Bucky LP. Reliable soft tissue augmentation: A clinical comparison of injectable soft-tissue fillers for facial-volume augmentation. *Ann Plast Surg.* 2005; 55(1):30–5.
16. Narins RS, Bowman PH. Injectable skin fillers. *Clin Plast Surg.* 2005; 32(2):151–62.
17. Rohrich RJ, Ghavami A, Crosby MA. The role of hyaluronic acid fillers (Restylane) in facial cosmetic surgery: Review and technical considerations. *Plast Reconstr Surg.* 2007; 120(6 Suppl):41S–54S.
18. Galderma Data on File 2014.
19. Scaperrotta G, Satchithananda K, Tengvar M, et al. Radiological assessment of the breast following enhancement with Macrolane: Managing the challenges. *Eur J Radiol.* 2017; 86:58–62.
20. Alijotas-Reig J, Fernández-Figueras MT, Puig L. Inflammatory, immune-mediated adverse reactions related to soft tissue dermal fillers. *Semin Arthritis Rheum.* 2013; 43(2):241-58.
21. Goisis M, Savoldi A, Guareschi M. Is hyaluronic acid gel a good option for breast augmentation? *Aesthetic Plast Surg.* 2011; 35(1):134-136.
22. Siebert T, Chaput B, Vaysse C, et al. The latest information on Macrolane™: Its indications and restrictions. *Ann Chir Plast Esthet.* 2014; 59(2):e1–e11.
23. D'Aniello C, Cuomo R, Grimaldi L, et al. Superior Pedicle Mammaplasty without Parenchymal Incisions after Massive Weight Loss. *J Invest Surg.* 2017; 30(6):410-420.
24. Casella D, Di Taranto G, Marcasciano M, et al. Evaluation of Prepectoral Implant Placement and Complete Coverage with TiLoop Bra Mesh for Breast Reconstruction: A Prospective Study on Long-Term and Patient-Reported BREAST-Q Outcomes. *Plast Reconstr Surg.* 2019; 143(1):1e-9e.
25. Tarallo M, Cigna E, Fino P, Lo Torto F, Scuderi N. La terapia chirurgica della gigantomastia [Macromastia surgical therapy]. *Ann Ital Chir.* 2011; 82(3):191-195.
26. Becchere MP, Farace F, Dessena L, et al. A case series study on complications after breast augmentation with Macrolane™. *Aesthetic Plast Surg.* 2013; 37(2):332-5.
27. McCleave MJ. Is Breast Augmentation Using Hyaluronic Acid Safe? *Aesthet Plast Surg.* 2010; 34(1):65-8; discussion 69-70.
28. Ribuffo D, Lo Torto F, Atzeni M, Serratore F. The effects of postmastectomy adjuvant radiotherapy on immediate two-stage prosthetic breast reconstruction: a systematic review. *Plast Reconstr Surg.* 2015; 135(2):445e.
29. Casella D, Di Taranto G, Marcasciano M, et al. Nipple-sparing bilateral prophylactic mastectomy and immediate reconstruction with TiLoop® Bra mesh in BRCA1/2 mutation carriers: A prospective study of long-term and patient reported outcomes using the BREAST-Q. *Breast.* 2018; 39:8-13.
30. Calabrese C, Casella D, Di Taranto G, et al. Oncoplastic conservative surgery for breast cancer: long-term outcomes of our first ten years experience. *Eur Rev Med Pharmacol Sci.* 2018; 22(21):7333-7342.