Journal of Plastic, Reconstructive & Aesthetic Surgery (2018) 71, 785–787

JPRAS
An International Journal of Surgical Reconstruction
www.JPRASurg.com

Editorial

EURAPS Editorial: BIA-ALCL, a brief overview

The history of breast implants includes important technological breakthroughs, but also safety controversies such as the 1992 FDA moratorium against silicone, the 2010 PIP implant scandal, and the 2015 Silimed ban.[1–3] Nevertheless, the popularity of breast augmentation continues to grow, and millions of patients receive breast implants each year.[4]

In 2011, history repeated itself when the Food and Drugs Association (FDA) announced that breast implants may be directly implicated in the aetiopathogenesis of Breast Implant Associated Anaplastic Large Cell Lymphoma (BIA-ALCL).[5] What started with sporadic case reports, soon became a cascade of events culminating in a second FDA announcement in 2016 and the World Health Organisation reclassifying lymphoid neoplasms to include BIA-ALCL as a distinct pathology.[6–8] Other national and international authorities then sought to promote awareness and reporting of new cases,[9,10] with a lead taken by Australasian surgeons to specifically include BIA-ALCL in the process of informed consent and preoperative counselling (78% compliance vs. France 46%, U.K. 41%, Italy 31%, and U.S.A. 24%).[11]

The Manufacturer and User Facility Device Experience (MAUDE) database of the FDA, the European task force for ALCL formed by the National Competent Authorities (NCAs), the Patient Registry and Outcomes for Breast Implants and ALCL Ethiology and Epidemiology (PROFILE) registry, and others offer a place for centralized data collection. Yet the aforementioned registries are full of poorly reported cases missing essential information (implant type, immunohistochemistry results etc.), and many countries have yet to present a single case, making estimation of BIA-ALCL prevalence more reliable than incidence.[12] Nevertheless, a Danish epidemiological study, showed that the cumulative risks in women with implants is 29 per million at 50 years and 82 per million at 70 years of age, and a recent study by the Italian Ministry of Health estimated the incidence in 2015 of 28 cases per 1 million.[13,14]

Despite this, only since 2011 plastic surgeons internationally agreed and promoted diagnostic and management guidelines that are nowadays widely accepted: all late onset seromas must be aspirated under ultrasound-guidance, with mandatory cytology and CD30+ immunohistochemistry to seek a diagnosis of BIA-ALCL. Cases of BIA-ALCL should be managed by surgical removal of the implant, seroma, and periprosthetic capsule; chemotherapy considered according to disease extension.[6] Most plastic surgeons are now aware of the condition and of its diagnosis and management, and it is now necessary to investigate the mechanism of its aetiology.[15]

Various aetiopathogenetic theories have been proposed, the immunology hypothesis, tribology, and subclinical infection being the most prevalent ones. All share chronic inflammation as a pathogenic mechanism. The immunology hypothesis, refers to silicone particulate release from the peaks of macrotextured implants generating intracapsular foreign bodies that results in a chronic immunologically driven inflammatory foreign body response, causing tissue growth at the periprosthetic capsule. When captured by macrophages silicone particles ignite a complex specific antigen-driven local Th1/Th17 immune response with involvement of the specific cytokines, interleukin-17, -6 and -8, transforming growth factor-ß1, and interferon, that leads to proliferation of the T cells with oncogenic mutation, through aberrant activation of STAT3, causing BIA-ALCL.[16–18] The second hypothesis comes from tribology (the science studying the interaction of surfaces in relative motion), and is that aggressively textured implants cause delamination of the periprosthetic capsule through mechanical tear stress[19] possibly responsible for double capsule phenomenon but also for unresolved inflammation, with genetic instability and activation of maladaptive homeostatic responses and dormant transcription factors.[20] The subclinical infection hypothesis is very intriguing and is supported by studies demonstrating the prevalence of a specific group of bacteria, Ralstonia spp. isolated on BIA-ALCL capsules, with some commentators incriminating specifically Ralstonia Pickettii without sufficient support.[21,22] However questions remain inadequately answered, such as why biofilm present on all devices yet ALCL only occurs around in textured breast implants; why biofilm increase is directly related to degree of capsular contracture, but not to sterile seroma presence in 80% of BIA-ALCL; why Ralstonia spp. is present, although at lower concentration, in non-ALCL capsules; and finally why prevalence of BIA-ALCL is comparable between aesthetic and reconstructive cases despite inability to respect the 14 points against infection in reconstruction.[22–25]

https://doi.org/10.1016/j.bjps.2018.04.012

A contrasting paradigm presented by some authors is that BIA-ALCL is not a cancer, but rather is a lymphoproliferative disorder that can regress spontaneously.[23] Two supporting cases are reported in which BIA-ALCL, diagnosed by standard preoperative aspiration and seroma cytology, was found absent on formal histology of the residual serum and capsule after treatment by implant removal and total capsulectomy (CD30+ lymphocytes not identified). Here the term "resolution" may simply be a misinterpretation of the time course of the disease, since indolent behaviour is reported in 2 cases of stage 1 BIA-ALCL such that after draining the CD30+ lymphocytes containing seroma they have not yet significantly repopulated. True resolution could only be considered if implant removal had not been performed and recurrence was shown not to have occurred after several years of careful follow up.[23] It is highly likely that BIA-ALCL occurred prior to the current diagnostic criteria being established, but were unintentionally treated successfully by surgeons following standard principles of seroma aspiration and/or capsulectomy without cytology or histology exams. The increase in BIA-ALCL cases over the last 10 years may simply reflect the increased use of macrotextured implants, the time-lag from their insertion to BIA-ALCL development, and increased awareness by plastic surgeons.

Understanding of the relation between BIA-ALCL and breast implant design will help us to better treat our patients, most particularly by assessing reported cases with either extremely early onset (4month) or without initial seroma (20%), and investigating the role and the fate of CD30 negative seromas. This step is fundamental to make implant surgery safer, and requires co-ordination between Competent Authorities, industry, and scientists. Industry must critically reassess breast implant manufacturing materials and processes, most critically as regards shell surfaces and texturing. Research should shift its focus to investigate control of the foreign body reaction by the development of biomimetic surfaces leading to a more biocompatible implant.[26] Finally, the cellular immune response must be investigated for therapeutic immunomodulatory targetting.[27]

In conclusion, BIA-ALCL should be openly assessed by all the involved actors, without fear of retribution. Plastic surgeons must report to respective National Competent Authorities all cases with complete information, which must then be shared at an international level; patients must pre-operative counselling about BIA-ALCL and its possible occurrence after breast implant surgery, followed-up and investigated accordingly; research must establish risk stratification data; and patient management should then include preventative measures, and BIA-ALCL specific surgical and medical treatment protocols when disease occurs.

References

1. Institute of Medicine Committee on the Safety of Silicone Breast Implants. In: Ernster V, Herdman R, editors. *Safety of silicone breast implants 31 Stuart Bondurant*. 1999.
2. Martindale V, Menache A. The PIP scandal: an analysis of the process of quality control that failed to safeguard women from the health risks. *J R Soc Med* 2013 May;**106**(5):173–7. doi:10.1177/0141076813480994. PubMed PMID: 23761525. PubMed Central PMCID: PMC3676226.
3. Medicines and Health Products Regulatory Agency. 2017. Available at: https://www.gov.uk/drug-device-alerts/implantable-medical-devices-manufactured-by-silimed-temporary-suspension-of-the-ce-certificate.
4. International Society of Aesthetic Plastic Surgery. *2015 global statistics*. 2016. Available at: http://www.isaps.org.
5. U.S. Food and Drug Administration. *FDA medical device safety communication: reports of anaplastic large cell lymphoma (ALCL) in women with breast implants*. Available at: http://www.fda.gov/medicaldevices/safety/alertsandno-tices/ucm240000.htm.
6. Santanelli di Pompeo F, Laporta R, Sorotos M, et al. Breast implant-associated anaplastic large cell lymphoma: proposal for a monitoring protocol. *Plast Reconstr Surg* 2015 Aug;**136**(2):144e–151e. doi:10.1097/PRS.0000000000001416. PubMed PMID: 26218387.
7. U.S. Food & Drug Administration (FDA). *Medical device reports of breast implant-associated anaplastic large cell lymphoma*. Silver Spring, Maryland. 2017. Available at: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm481899.htm.
8. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 2016;**127**(20):2375–90. http://doi.org/10.1182/blood-2016-01-643569.
9. French National Agency for Medicines and Health Product Safety. *Update on BIA-ALCL*. Available at: http://ansm.sante.fr/var/ansm_site/storage/original/application/e91b9eef26804c584537747474062bf8.pdf [Accessed 30 January 2017].
10. Italian Ministry of Health. *Recommendations*. Available at: http://www.salute.gov.it/portale/temi/p2_6.jsp?lingua=italiano&id=4419&area=dispositivi-medici&menu=vigilanza [Accessed 30 January 2017].
11. Pittman TA, Fan KL, Rudolph MA. Anaplastic large cell lymphoma: emerging consent and management patterns among American and International Board Certified Plastic Surgeons. *Plast Reconstr Surg* 2016 Nov;**138**(5):811e–818e. PubMed PMID: 27782987.
12. Srinivasa DR, Miranda RN, Kaura A, et al. Global adverse event reports of breast implant-associated ALCL: an international review of 40 government authority databases. *Plast Reconstr Surg* 2017 May;**139**(5):1029–39. doi:10.1097/PRS.0000000000003233. PubMed PMID: 28157770.
13. de Boer M, van Leeuwen FE, Hauptmann M, et al. Breast implants and the risk of anaplastic large-cell lymphoma in the breast. *JAMA Oncol* 2018;**4**(3):335–41. doi:10.1001/jamaoncol.2017.4510. Mar 1, PubMed PMID: 29302687.
14. Campanale A, Boldrini R, Marletta M. 22 cases of breast implant-associated ALCL: awareness and outcome tracking from the Italian ministry of health. *Plast Reconstr Surg* 2018 Jan;**141**(1):11e–19e. doi:10.1097/PRS.0000000000003916. PubMed PMID: 29280858.
15. Clemens MW, Brody GS, Mahabir RC, Miranda RN. How to diagnose and treat breast implant-associated anaplastic large cell lymphoma. *Plast Reconstr Surg* 2018 Apr;**141**(4):586e–599e. doi:10.1097/PRS.0000000000004262.
16. Bizjak M, Selmi C, Praprotnik S, et al. Silicone implants and lymphoma: the role of inflammation. *J Autoimmun* 2015 Dec;**65**:64–73. doi:10.1016/j.jaut.2015.08.009. PubMed PMID: 26330346. Epub 2015 Aug 29, Review.
17. Wolfram D, Rabensteiner E, Grundtman C, et al. T regulatory cells and TH17 cells in peri-silicone implant capsular fibrosis. *Plast Reconstr Surg* 2012 Feb;**129**(2):327e–337e. doi:10.1097/PRS.0b013e31823aeacf. PubMed PMID: 22286447.
18. Di Napoli A, Jain P, Duranti E, et al. Targeted next generation sequencing of breast implant-associated anaplastic large cell lymphoma reveals mutations in JAK/STAT signalling pathway genes, TP53 and DNMT3A. *Br J Haematol* 2018 Mar;**180**(5):

741–4. doi:10.1111/bjh.14431. PubMed PMID: 27859003. Epub 2016 Nov 10.
19. Giot JP, Paek LS, Nizard N, et al. The double capsules in macrotextured breast implants. *Biomaterials* 2015 Oct;**67**:65–72. doi:10.1016/j.biomaterials.2015.06.010. PubMed PMID: 26210173. Epub 2015 Jun 23.
20. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis* 2009 Jul;**30**(7):1073–81. doi:10.1093/carcin/bgp127. PubMed PMID: 19468060. Epub 2009 May 25, Review.
21. Hu H. Chronic biofilm infection in breast implant is associated with an increased T-cell lymphocyte infiltrate: implication for breast implant associated lymphoma. *Plast Reconstr Surg* 2014 January;319–29.
22. Brody GS. The case against biofilm as the primary initiator of breast implant-associated anaplastic large cell lymphoma. *Plast Reconstr Surg* 2016 Apr;**137**(4):766e–767e. doi:10.1097/01.prs.0000480003.80422.03. PubMed PMID: 26809044.
23. Fleming D, Stone J, Tansley P. Spontaneous regression and resolution of breast implant- associated anaplastic large cell lymphoma: implications for research, diagnosis and clinical management. *Aesthetic Plast Surg* 2018;**100**(2):1–7. doi:10.1007/s00266-017-1064-z.
24. Deva AK, Adams WP Jr, Vickery K. The role of bacterial bio lms in device-associated infection. *Plast Reconstr Surg* 2013;**132**:1319–28.
25. Sorotos M, Longo B, Amorosi V, Santanelli di Pompeo F. Reply: macrotextured breast implants with defined steps to minimize bacterial contamination around the device. Experience in 42,000 implants. *Plast Reconstr Surg* 2018;**141**(9):[Correspondence].
26. Alexandre MM, Santanelli di Pompeo F, De Mezerville R. Nanotechnology, nanosurfaces and silicone gel breast implants: current aspects. *Case Reports Plast Surg Hand Surg* 2018;99–113. doi:10.1080/23320885.2017.1407658.
27. Di Liddo R, Valente S, Taurone S, et al. Histone deacetylase inhibitors restore IL-10 expression in lipopolysaccharide-induced cell inflammation and reduce IL-1β and IL-6 production in breast silicone implant in C57BL/6J wild-type murine model. *Autoimmunity* 2016;**31**:1–11. doi:10.3109/08916934.2015.1134510.

Fabio Santanelli di Pompeo
EURAPS European Association of Plastic Surgeons, Rome, Italy
"Sapienza" University of Rome, School of Medicine and Psychology, School program in Plastic Reconstructive and Aesthetic Surgery, Rome, Italy
Plastic Surgery Unit, Sant'Andrea Hospital, Via di Grottarossa 1035-39, 00189 Rome, Italy

Michail Sorotos
Plastic Surgery Unit, Sant'Andrea Hospital, Via di Grottarossa 1035-39, 00189 Rome, Italy

E-mail address: fabio.santanelli@uniroma1.it