INTERNATIONAL CONFEDERATION OF PLASTIC SURGERY SOCIETIES

Facts, Figures and Practical Guidelines in ALCL

Breast Implant Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) in daily practice.

Items of Note for Your Patients:

- How do you **recognize it**? Unexplained seroma in a breast with an implant.
- How do you **diagnose it**? Ultrasound guided aspiration and cytological analysis.
- When sending fluid for cytology, consider asking for identification of cytological markers CD30, ALK.
- **Discuss** BIA-ALCL signs and symptoms in your informed consent for new patients
- Most experts advise using a smooth implant or autologous techniques for new implant recipients.
- Early detection and treatment before dissemination is key.

Report your case into the Patient Registry and Outcomes For breast Implants and anaplastic large cell Lymphoma (ALCL) etiology and Epidemiology (PROFILE) registry, https://www.thepsf.org/research/registries/profile/case-submission

The FDA has clear recommendations for clinicians:

- Be aware that most **confirmed** cases of BIA-ALCL have occurred in women with textured breast implants. Provide the manufacturers' labeling as well as any other educational materials to your patients before surgery and discuss with them the benefits and risks of the different types of implants.
- Consider the possibility of BIA-ALCL when you have a patient with late onset, persistent peri-implant seroma. In some cases, patients presented with capsular contracture or masses adjacent to the breast implant. If you have a patient with suspected BIA-ALCL, refer her to an appropriate specialist for evaluation. When testing for BIA-ALCL, collect fresh seroma fluid and representative portions of the capsule and send for pathology tests to rule out BIA-ALCL. Diagnostic evaluation should include cytological evaluation of seroma fluid with Wright Giemsa stained smears and cell block immunohistochemistry testing for cluster of differentiation (CD) and Anaplastic Lymphoma Kinase (ALK) markers.
- Develop an individualized treatment plan in coordination with the patient's multi-disciplinary care team. Consider current clinical practice guidelines, such as those from the Plastic Surgery Foundation or the National Comprehensive Cancer Network (NCCN) when choosing your treatment approach.
- Report all confirmed cases of ALCL in women with breast implants to the FDA. In some cases, the FDA may contact you for additional information. The FDA will keep the identities of the reporter and the patient confidential.
- Submit case reports of BIA-ALCL to the PROFILE Registry to contribute to a better understanding of the causes and treatments of BIA-ALCL. *(https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239995.htm*

Findings of the European Commission, the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) Report April 2017

Following the request received from the European Commission, the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) performed a literature search and launched a call for information to gather new scientific information related to a possible association between breast implants and anaplastic large cell lymphoma (ALCL).

The scientific information retrieved from the literature search and the call for data shows that over the past years a body of medical literature on a possible association between breast implants and ALCL has been published. However, it consists mainly of case reports, case series and few observational epidemiologic studies.

Based on the evaluation of this scientific information, the SCHEER acknowledges that there have been new documented cases of ALCL in women with breast implants, worldwide, suggesting a breast implant – ALCL association.

The SCHEER concludes that there is currently insufficient scientific information available to establish a methodologically robust risk assessment to investigate a possible association of breast implants with ALCL development.

It is highlighted that there is an emerging need for prospective studies in order to be able to perform a more robust evaluation of the possible association between breast implants and ALCL.

Moreover, the lack of registries, throughout the world, of women with breast implants is a major challenge for providing evidence-based conclusions on the potential association between breast implants and ALCL. Such registers, and their systematic evaluations, are urgently needed.

The available information that has already been collected, together with the most recent 2017 publications, suggests that there may be such an association. Therefore, the SCHEER recommends a more in-depth evaluation on the possible association between breast implants and ALCL.

A mammogram is in most of the cases the first imaging approach performed, whereas, ultrasound is subsequently performed and analysed in conjunction with the mammogram's findings. However, the imaging findings of ALCL are often very non-specific (Letter et al., 2016).

Some investigators suggest that there is a need for standardised criteria to clinically diagnose ALCL, a need to identify risk factors and a need to update the evaluation of imaging studies, (ultrasound, computerised tomography, magnetic resonance imaging or positron emission tomography, mammography) to diagnose ALCL (Miranda, 2014; Mazzucco, 2014; Adrada et al., 2014). In a review paper, Adrada et al., (2014) concluded that current imaging with ultrasound, computerised tomography, magnetic resonance imaging or positron emission tomography appears suboptimal in the detection of an abnormality associated with a silicone breast implant. Therefore, it is possible that ALCL has been and continues to be under-diagnosed.

In conclusion, the evidence emphasises the need for a better understanding of the complementary role of imaging results regarding the diagnosis of ALCL.

Registries with detailed data on disease patho-biology and associated factors are powerful tools to track, study, and manage chronic diseases. The need for establishing robust registries for breast implant-associated pathologies has been suggested by several investigators (Evans et al., 2011; Cooter et al., 2015; Brown et al., 2016).

There are some registries evaluating the clinical outcomes of silicone breast implants. For example, the International Collaboration of Breast Registry Activities (i.e., ICOBRA) involves the national plastic

surgery societies of Australia, Austria, Canada, France, Germany, Ireland, Italy, the Netherlands, New Zealand, South Africa, the United Kingdom and the US, and was developed to "establish an internationally agreed and comparable minimum data set, made up of standardised and epidemiologically sound data that reflect global best Final Scientific advice on the state of scientific knowledge regarding a possible connection between breast implants and anaplastic large cell lymphoma.

Practice"13. In the US, a collaborative project has been established, with the American Society of Plastic Surgeons and the Plastic Surgery Foundation, in order to collect data through the Patient Registry and Outcomes for Breast Implants and Anaplastic Large Cell Lymphoma Etiology and Epidemiology (i.e. the PROFILE Registry). In France there is the national network of experts LYMPHOPATH, which is a government-supported network that aims to review lymphoma diagnoses or suspected lymphoma diagnoses; since 2010, 43,830 lymphomas have been registered in the database of the LYMPHOPATH network (Laurent et al., 2016). In the Netherlands, the Dutch Breast Implant Associated ALCL Consortium, consisting of a multidisciplinary group of scientists, is investigating ALCL occurrences in women with breast implants14.

In 2015, a study in 11 countries, illustrating different data collection systems and registries around the world, revealed that less than half of the participating countries had operational registries and that none of these had adequately high data capture to allow for a reliable outcome analysis. The study also revealed that the two most common problems that discouraged participation were the complexity of data sets and the opt-in consent model (Cooter et al., 2015).

In a recent review of federal implantable device regulatory bodies and databases for 40 countries (Srinivasa et al, 2017), it was noted that "international multi-institutional collaborations and centralized tissue consortiums working in concert with federal authorities are necessary to acquire accurate complete data on breast implant-associated ALCL".

All of the above underline the need for registries, throughout the world, with clinical data of women with breast implants. Using the accumulated information of these registries is a major challenge for providing evidence-based conclusions in the potential association between breast implants and ALCL.

https://ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/scheer_o_007.pdf

Resources and Practical Algorithms:

ASPS/ASAPS algorithm and advice: https://www.surgery.org/downloads/private/joint-asps-asaps-statement-on-breast-implant-associated-alcl.pdf

The French National Cancer Institute: breast implant-associated anaplastic large cell lymphomas

Profile website: https://www.thepsf.org/research/registries/profile

SCHEER Report April 2017:
https://ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/scheer_o_007.pdf

Australian TGA advice: https://www.tga.gov.au/alert/breast-implants-and-anaplastic-large-cell-lymphoma#hp