

Association Between Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) Risk and Polyurethane Breast Implants: Clinical Evidence and European Perspective

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Abstract

This article aims to present an overview on the use of polyurethane (PU) breast implants and the possible association with the risk of developing breast implant-associated anaplastic large cell lymphoma (BIA-ALCL), with a special look at the current situation in Europe. It is well known that the real cause of BIA-ALCL remains unknown. Although this is a rare disease, many interesting theories surrounding its development have been advanced; however, none of these theories has been able to demonstrate with statistical significance, as required by the criteria of evidence-based medicine, definitive clinical proof as to why BIA-ALCL develops. It is widely assumed that the implant surface plays a crucial role. Most BIA-ALCL cases are associated with macro-textured implants, but from a strictly scientific point of view, this link is not supported by any clear clinical evidence. A deeper discussion of the various implant surfaces indicates that adding further categories to the existing surface classification (smooth, micro-, and macro-textured) should be avoided. Moreover, one of the most common misunderstandings should be clarified: PU breast implants cannot be classified as macro-textured implants. The PU foam that covers breast implants provides a completely different surface, and the mechanisms of action related to tissue adhesion, as well as to fibrous capsule formation, differ substantially from those of smooth or textured implants.

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Introduction and Explanation of Important Basic Concepts

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a rare type of non-Hodgkin's lymphoma, as provisionally defined by the World Health Organization (WHO) in 2016,¹ that can occur in women after cosmetic or reconstructive surgery with breast implants.

This classification of non-Hodgkin's lymphoma is derived from a few retrospective cases collected via different methods rather than from prospective or case-controlled studies, as required by evidence-based medicine.²

BIA-ALCL is an anaplastic lymphoma kinase (ALK) lymphoma characterized by a monoclonal expansion of CD30+ large anaplastic cells mostly confined to the peri-implant

seroma fluid. However, some cases of solid infiltrating masses with an aggressive clinical course have been reported.³

The current evidence from peer-reviewed literature is insufficient to establish any significant link between the development of BIA-ALCL and surgical technique or type of patient. One of the most attractive existing theories suggests a genetic predisposition because JAK-STAT signaling pathway

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Table 1. Surface Descriptions Based on the Average Roughness* Measurement on the Finished Device

Type of surface	Roughness (μm)
Smooth	<10
Micro-textured	10–50
Macro-textured	>50

*The average roughness is measured as Ra or Sa.

genes have been found to be mutated in some BIA-ALCL specimens.⁴ The ability to reduce the risk of BIA-ALCL through the use of specific surgical techniques has not yet been established with statistical evidence, although a reduction in the incidence of this disease based on the use of certain elements of Good Clinical Practice (GCP) has been proposed.⁵

It is necessary to mention 2 other frequently cited hypotheses on the development of BIA-ALCL, which are also associated with the hypotheses described above. The first theory suggests that there is an immune system response to chronic inflammation induced by silicone particulates or other factors.⁶ The second theory suggests the presence of a biofilm with a high bacterial load of Gram-negative and rod-shaped bacteria.⁷ However, there is no real clinical evidence to prove that contamination by Gram-negative bacteria (such as *Ralstonia pickettii*) could be responsible for the onset of a malignancy. Indeed, most cases of BIA-ALCL do not show a high presence of Gram-negative bacteria such as *R. pickettii*.⁸

For the purposes of this work, it is necessary to clarify the classification of implant surfaces. In April 2018, the new edition of the approved ISO standard was published.⁹ Appendix H of these new ISO guidelines provides precise definitions for the surfaces of mammary implants (as summarized in Table 1). In light of the publication of this official document, it is difficult to understand why several authors worldwide have felt the need to publish different surface classifications based on personal opinions.

Polyurethane (PU)-coated implants are mistaken for textured implants in several articles published in various journals, including indexed journals with a high impact factor. Implant texturing is a surface irregularity on the silicone shell, designed to mimic the shape and confer the benefits of PU implants in terms of reduced complications.

Several references (eg, Vázquez¹⁰ and Castel et al¹¹) have described the different mechanisms of action of PU implants. PU implants cannot be classified as macro-textured implants, because the PU foam that covers the silicone implant is a 3-dimensional matrix that is incorporated into the shell and becomes, after some years, an integral part of the capsule (Figure 1). This is the reason why, for instance, the low incidence of capsular contracture (CC) does not diminish over time. This attribute and others, such as strong tissue adhesion and the lack of dislocation,

have been described multiple times in the literature since 1972.^{10–15}

The Use of PU Implants and an Eventual Increased Risk of BIA-ALCL: Does This Association Really Exist?

The core message of this text is that literature reports of an increase in the incidence of BIA-ALCL associated with the use of PU implants should be reviewed, and it is also necessary to clarify whether this literature is supported by a proper level of statistical significance.

A paper published in 2017 states that the higher the surface area of the textured implants, the greater the risk of BIA-ALCL.¹⁶ Assuming, as these authors did, that PU implants are macro-textured, their increased surface area should cause a higher incidence of BIA-ALCL than either micro- or macro-textured implants. However, surprisingly, their data prove exactly the opposite: the higher surface area of the PU implants does not cause a higher number of BIA-ALCL cases.

In order to identify a unified hypothesis to explain the phenomena surrounding BIA-ALCL, the authors additionally assume that inflammation is the likely initiator of this disease. The presence of chronic bacterial biofilm infection is likely the cause of this inflammation. Citing several clinical papers to support this thesis, these investigators state that textured implants, with their greater surface area, promote higher levels of bacterial growth and that this produces a linear increase in lymphocyte activation. They also report that PU implants are associated with a significantly higher level of bacterial contamination in human CC.

Nevertheless, an analysis of the literature indicates there is no clinical evidence to prove the hypothesis that a higher bacterial load leads to a higher risk of BIA-ALCL. It is instead proven that infection of breast implants by the formation of a bacterial biofilm is a significant potentiator of CC with silicone-textured implants.

The literature on PU implants shows the opposite. In fact, it has been reported that PU implants have a higher infiltration of inflammatory cells but no signs of acute infection or positive bacterial growth compared with textured implants, suggesting that the larger surface area of the PU foam creates no higher risk of a biofilm surrounding the capsule.¹⁷

Another important finding for which no scientific explanation exists is the varying geographic distribution of BIA-ALCL: a US epidemiologic study disclosed a lifetime prevalence of 33 cases of BIA-ALCL per 1 million people with textured breast implants.¹⁸ The Australian literature (already described) reports a higher incidence than in the United States; however, there are almost no reported cases in Asia and just a few in Latin America. What are the reasons for this inexplicable geographic distribution? The most likely reason is that some cases outside the United States have not been reported or

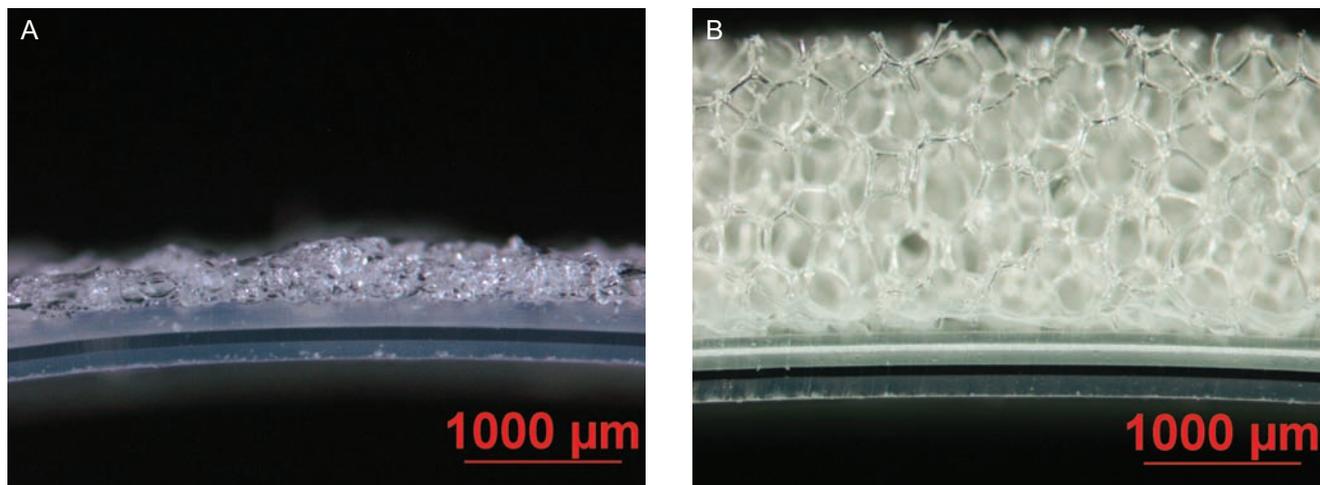


Figure 1. Lateral views taken with light microscopy demonstrating the difference between (A) a textured implant and (B) a polyurethane implant.

have been misdiagnosed or undiagnosed. Many questions remain unanswered.

Even within Europe there are huge differences regarding the incidence of BIA-ALCL between countries. As of June 2018, the Medicines and Healthcare products Regulatory Agency in the United Kingdom has received 48 reports of ALCL in patients with breast implants, 40 of which meet the WHO diagnostic criteria for BIA-ALCL.¹⁹ The French authorities informed the scientific community confidentially that they had collected 50 BIA-ALCL cases up to June 2018 (data not shown). Twenty-two cases of BIA-ALCL in Italy were published in 2018, based on data from the Italian Ministry of Health.²⁰ In the Netherlands, at the beginning of 2018, de Boer et al²¹ reported that of 43 patients with BIA-ALCL, 32 had breast implants. These authors were able to calculate the relative and absolute risk of BIA-ALCL by creating a control group that comprised all the patients with breast lymphoma, but not BIA-ALCL. With this approach, they achieved statistical significance for their findings. De Boer et al state clearly that, despite most BIA-ALCL cases being associated with macro-textured implants from various suppliers, this lymphoma has also been observed in patients with micro-textured implants, both in their study and by others, as well as possibly in smooth implants. This is in stark contrast to the position of the US Food and Drug Administration (FDA). The FDA's latest update, released in March 2018 (Figure 2), reported 30 cases of BIA-ALCL with smooth implants; however, there was no adequate history for these implants, and therefore according to the FDA, BIA-ALCL cannot currently be definitively associated with smooth implants.²²

The following statement should be considered a personal opinion, because it lacks proper clinical evidence; however, the reasoning is supported by an accurate analysis of market shares over time. Since the early 1990s, the ratio of worldwide sales of smooth and textured implants has always been approximately 85% to 90% textured and 10% to 15% smooth. This is still the case today. Therefore, the fact

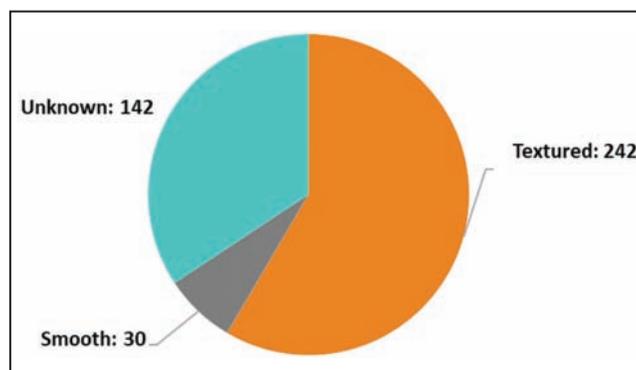


Figure 2. Anaplastic large cell lymphoma cases based on the US Food and Drug Administration update issued in March 2018.

that there are more BIA-ALCL cases with textured than with smooth implants is normal, because approximately 85% more textured implants are sold worldwide than smooth implants. Moreover, according to current scientific knowledge, it is not possible to claim that any kind of implant will never face ALCL issues due to its specific characteristics.

Returning to the European situation, one of the most controversial issues is precisely that of geographic discrepancy. In addition to the high or relatively high number of cases in the countries described above, there are countries (sometimes small) that may well not consistently report BIA-ALCL cases to the competent authorities, even though they actually have a very low BIA-ALCL incidence. There is one country, for instance, that represents this situation well: Germany. This is a large and well-evolved country both from social and scientific points of view, and it is therefore impossible to imagine that the surgeons or the breast implant manufacturers are not reporting all BIA-ALCL cases to the proper government authorities. Nevertheless, the latest figures from the Federal Institute for Drugs and

Medical Devices for the entire country indicate 7 cases of BIA-ALCL (<https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239995.htm>; Accessed August 28, 2018). In addition, this is the only European country that hosts a producer of PU implants (POLYTECH Health & Aesthetics, Dieburg, Germany), whose textured and PU breast implants have a large market share.

Therefore, although some authors have reported an association between the use of PU implants and the risk of BIA-ALCL, this is clearly refuted by the clinical evidence (no clinical paper proposing this theory reaches the minimum level of statistical significance) and by the fact that there is no reported case of ALCL after a primary breast surgery with PU implants in Germany or in any other European country. There are only a few cases of late seroma that are still under investigation.

Of course, the aim of this assertion is not to declare that PU implants pose no risk of causing the development of BIA-ALCL; to date, there is 1 confirmed case of BIA-ALCL with a PU POLYTECH (POLYTECH, health & Aesthetics, Dieburg, Germany) implant and several cases with PU Silimed (Silimed Inc., Dallas, Texas, United States) implants in Australia, in addition to 1 recent case of a PU POLYTECH implant that is still under investigation in Belgium. The aim of this assertion is also not to put the blame only on macro-textured implants. However, it is important to repeat that, according to evidence-based medicine, the causal relation between the surface of breast implants and the increased risk of BIA-ALCL remains unclear.

It should be recognized that there are 2 types of PU breast implants (those from Silimed and those from POLYTECH) that behave differently because of the use of different silicone materials and the methods used to embed the PU foam into the silicone shell of the implants. There is no proof that both methods provide similar durability for the attachment of the PU to the silicone shell; however, many cases of delamination have been reported with PU Silimed implants. With early delamination of the PU foam, an inadequate tissue ingrowth and incomplete immobilization of the implant could occur, in addition to the exposure of the textured surface or the release of bacteria previously sequestered in PU microcapsules. It is not known whether these topics will be relevant, but due to the fact that the etiology of BIA-ALCL is still unknown, every detail should be divulged (Figure 3).

Further Considerations for Continuous Medical Education

The aim of this article is not to provide surgeons with further guidelines for the evaluation, diagnosis, treatment, and surgical plan for patients with suspected BIA-ALCL. Other authors have already done this very well,²³ even though some have described certain assumptions as certainties. It



Figure 3. An early delamination of a polyurethane Silimed breast implant (courtesy of Daniel Fleming, MD, Brisbane, Australia).

is strongly advocated that all of these guidelines and GCP be followed conscientiously for sake of the patient's health, thereby avoiding the spread of fear and false statements; the risk of such behavior is that a woman who has undergone a mastectomy after cancer will reject breast reconstruction. The patient has to know, as Clemens and other authors have repeatedly noted, that the risk of death is extremely rare when BIA-ALCL is treated in a timely fashion. Each surgeon should not only avoid changing his or her usual surgical practice, but also pay close attention to any sudden swelling of an implanted breast; in addition, after reporting the case, the surgeon must treat the patient according to the suggested guidelines (removal of the implant and total capsulectomy).

A proper scientific approach involves expressing doubts that stimulate further investigations. However, what role do plastic or cosmetic surgeons play in supporting their peers and helping in the management of this new challenge? First, the surgeon has a primary and instrumental role: to report all the cases of diagnosed BIA-ALCL and to remember that it is his or her duty to complete all of the possible tests, even when there is only a small doubt. Secondly, surgeons must be aware that they cannot perform all the research alone: this is the era of multidisciplinary teams, in all medical and clinical areas. If BIA-ALCL is at any stage a rare type of non-Hodgkin's lymphoma, as defined by WHO, then plastic surgeons, whether alone or in a group, will not be able to find the cause, the cure, and the way to prevent this disease. It should be noted here that hundreds of researchers around the world have for decades been studying the causes of blood cancers, and despite great advances, they have still not found a cure. A cancer, by its nature, usually develops following a series of chain reactions. Therefore, perhaps BIA-ALCL is also a multifactorial disease. When a surgeon wishes to support research about this disease, he or she has to begin with a mind full of unsolved questions,

and then ask for the help of other specialists—oncologists, pathologists, hematologists, immunologists, microbiologists, molecular and cellular biologists, and biostatisticians. Research has to be guided by one simple but essential goal: any laboratory outcome must correspond to real life.

Finally, it is important to realize that the reasoning of surgeons who discover opposing clinical evidence should always be listened to. For instance, the WHO classification has to be acknowledged and respected, but it is also the surgeon's duty to scrutinize new clinical evidence carefully. Indeed, based on the epidemiology supported by 2 case studies, Fleming et al²⁴ have challenged current views on BIA-ALCL diagnosis and treatment by showing that spontaneous regression and apparent resolution of BIA-ALCL can occur. This finding could have important implications for the research, diagnosis, and clinical management of BIA-ALCL. Nevertheless, a letter to the editor that refutes these findings has been published.²⁵ Maybe we need more evidence before asserting definitely that spontaneous regression and spontaneous remission can occur.

Moreover, looking even at nonrecent literature, it is possible to find completely different diseases but with the same markers for diagnosis as are found for BIA-ALCL. For instance, lymphomatoid papulosis (LyP) is a CD30+ and ALK- monoclonal T cell lymphoproliferative disorder that is histologically malignant and clinically benign. Even primary cutaneous ALCL (pc ALCL) is similar to BIA-ALCL with an infrequent spread and an excellent prognosis. pc ALCL can spontaneously revert to LyP, and both can spontaneously resolve.²⁶ As a result, can seroma-only BIA-ALCL be better described as a lymphoproliferative disorder? It is probable that BIA-ALCL represents a spectrum of diseases ranging from seroma-only disease to a malignant cancer. This question remains unanswered and requires deep reflection.

CONCLUSIONS

It is strongly suggested that surgeons continue to report each case of BIA-ALCL, and to read any clinical paper with an open mind but with their focus firmly on evidence-based medicine.

Following this independent and strictly scientific approach, it is crucial to emphasize that implants covered with PU foam should not be classified as macro-textured implants; in fact, these coated breast implants ensure a lower rate of CC and, according to the current knowledge, an even lower rate of BIA-ALCL. However, only complete integration of the PU foam with the implant surface can play an essential role in avoiding early delamination.

Regarding the real cause of BIA-ALCL, the only acceptable statement that can be agreed upon according to the current clinical evidence is that no conclusion can be drawn until a wide range of epidemiologic studies with statistically significant outcomes is published.

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