



# Update: Spontaneous Regression and Resolution of Breast Implant-Associated Anaplastic Large Cell Lymphoma—Implications for Research, Diagnosis and Clinical Management—Our Reflections and Current Thoughts Two Years On

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We are pleased to learn that our article was one of the most cited in the history of the journal. We wrote it because of the rapid rise in Australia of patients with seroma-only BIA-ALCL disease who were being told they had cancer when this did not accord with the evidence [1].

The article's hypothesis that not all patients with BIA-ALCL had an inevitable malignancy was founded on the observed epidemiology of BIA-ALCL. In summary, the rapid rise in diagnosis had mirrored the advent and increasing adoption of cytological testing for the disease. There was no reason to suppose that BIA-ALCL was not present with the same incidence in textured implant-related late seromas *prior* to the advent of cytological testing in 2008 as *afterwards*. Such implants were widely used in Australia for 16 years before the first case of BIA-ALCL was recognised. The median interval from implantation to diagnosis was 7–8 years, and cancer registry data showed no increase in the incidence of non-Hodgkin lymphoma in women in the period 2000–2013 [2].

The existence of spontaneous regression and spontaneous resolution is an explanation of what happened to the seroma patients who had undiagnosed BIA-ALCL prior to

the onset of cytological testing to look for it—they got better, often without surgical intervention [3, 4].

The two case studies in our article were presented as supportive clinical evidence, consistent with the hypothesis. Furthermore, an important context was provided that the WHO 2016 classification of BIA-ALCL as a new lymphoma was and remains *provisional* and therefore, by definition, is uncertain [5]. This fact had been and continues to be largely ignored by both the academic and lay media. Lastly and most importantly, we felt uncomfortable with the label of malignant 'lymphoma' for the non-invasive presentation that achieved 100% cure with surgery [6], especially when no residual disease was necessarily identifiable at that surgery. Whilst such perspectives did not accord with the then established view, it was for these fundamental reasons that our article might have been considered innovative and relevant.

The article received strong criticism in the form of subsequent published letters [7–10]. However, the correspondence focussed on the two case studies whilst failing to acknowledge and address the centrality of the epidemiological evidence to the hypothesis. Further, we were astonished to discover unpublished criticism that even included an allegation that the manuscript was fraudulent. This caused the withdrawal of an invitation to the primary author to present the paper at an international academic meeting. Thankfully, the allegation was easily disproved and the ethos of adherence to the scientific principle of open discussion prevailed. The invitation was graciously re-instated and the paper presented [11].

Since the publication of our article and consistent with its hypothesis, the number of cases of BIA-ALCL diagnosed and the proportion without invasive disease have continued to rise [12]. That spontaneous regression occurs

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is now beyond doubt. In Australia, a recent example is of a patient who had CD30 + atypical T cells present in a peritextured breast implant seroma in 2015. The sample was too small for ALK testing, and therefore, the pathologist reported she was unable to confirm or deny the presence of BIA-ALCL. The patient remained asymptomatic and untreated until 2019 when she underwent unrelated surgery for capsular contracture. Peri-implant fluid identified at surgery and capsular biopsies were negative for BIA-ALCL. The patient developed a postoperative seroma 7 weeks later which was retested and now positive for BIA-ALCL. Unless in 2015 the patient had the rare disorder systemic ALCL (which presented as a peri-implant seroma and spontaneously resolved) and then developed a different, also rare disease, BIA-ALCL, in 2019, it is undeniable that she had BIA-ALCL in 2015. The disease regressed, remained asymptomatic and was not present histopathologically in 2019 until seven weeks after she was exposed to a further inflammatory stimulus by means of the replacement surgery. The lack of symptoms and the absence of BIA-ALCL cells in specimens taken 4 years after such cells were present, put into perspective the speculative theoretical assertion that spontaneous regression is artefactual and explained by a temporary dilutional effect of seroma aspiration [7, 8, 12].

Persisting reluctance to accept that spontaneous regression of BIA-ALCL occurs can compromise research findings. At the time of publication of our article, the theory that surface area bacterial contamination was the cause of BIA-ALCL predominated [13]. This theory predicts that implants with the greatest surface area will have the highest incidence [14]. Whilst as yet unproven, for this hypothesis to be true requires that *all* polyurethane foam covered (PU) silicone breast implants will have the highest incidence of BIA-ALCL as they have the greatest degree of surface ‘texturing’. However, only one brand of PU implants, Silimed (Rio de Janeiro, Brazil), currently has such a reported increased incidence. For unrelated reasons, Silimed implants have not been available in Australia since 2015 and are known to cause inflammation through delamination of the PU foam layer and particle shedding, as a consequence of a manufacturing fault [15]. An example of delamination is shown in Fig. 1. The only other brand of PU implant that remained available, Polytech (Dieburg, Germany), does not have any such known manufacturing fault and has only a single case of BIA-ALCL in Australia and one other worldwide. Accordingly, it has been reported to have currently the *lowest* incidence of BIA-ALCL for a ‘textured’ implant [16]. This is at odds with the infection theory and unless numbers of cases of BIA-ALCL related to Polytech PU implants dramatically increase, the hypothesis that bacterial contamination proportionate to implant surface area is the cause of BIA-



**Fig. 1** Early delamination of polyurethane foam from a Silimed implant

ALCL will be disproved. Interestingly, we note increasing doubts about the infection theory and the evidence underpinning it have steadily emerged [17–19].

We note with concern that the recent case of BIA-ALCL described above is being reported as relating to the secondary implant replacement using a Polytech PU implant [20, 21]. In fact, as described above, there is proof the disease was, prior to its spontaneous regression, present 4 years before any exposure to that type of implant.

All patients with implants will inevitably be exposed to some form of biological mediator, either bacterial and/or viral, capable of mediating a lymphomatoid change at the cellular level. The highest incidence of BIA-ALCL is observed with salt-reduced macrot textured implants and delaminated, faulty Silimed PU implants, both of which are known to shed more particles than those implants with lower rates of BIA-ALCL [15, 22], including implants with similar surface areas. In that context, currently, the evidence supports a chronic inflammation exacerbated by particle shedding in genetically susceptible individuals [23, 24] as a cause, perhaps the cause, of BIA-ALCL.

Linked to the infection theory is a new classification system of breast implant outer shells, which assumes that PU implants are merely an incrementally more textured

implant [14]. Putting aside the necessity of yet further reclassification in the absence of demonstrable clinical validity [25], PU implants are a fundamentally different type of implant that behave in a very different way to an ordinary textured implant [15, 19, 26]. When spontaneous regression is denied and consequent misinformation published about BIA-ALCL in relation to properly constructed PU implants, this has the capacity to mislead. For example, the Therapeutic Goods Administration (TGA) in Australia has banned Polytech PU implants on the basis of a single case in Australia amongst a total of two in the world, apparently on the basis of an assumed ‘class effect’ relating to the faulty Silimed implants. Such a decision harms women and in Australia has condemned them to lose the benefits of more than 5 decades of related clinical data and experience with PU implants [27].

Whether spontaneous regression represents resolution in some patients remains unproven. The events described above, where a patient had a prolonged period of regression prior to the reappearance of BIA-ALCL cells, is relevant in this respect. The recurrence of disease does not necessarily imply malignancy. A recurrent non-invasive presentation may represent a persistence of the original lymphoproliferative process with the capacity to again regress. The mandatory curative surgery provided, correctly, to non-invasive disease patients may mask the answer to these questions for some time yet. Studies addressing the early steps in the pathogenesis of BIA-ALCL at the molecular and cellular levels and further epidemiological studies may provide the answer [28, 29]. The hypothesis that untreated seroma-only BIA-ALCL will always progress to invasive lymphoma and is therefore different to lymphomatoid papulosis (LyP) and primary cutaneous ALCL (pcALCL), the only other disease with identical cells, remains possible, but it did not fit the evidence when we published our article and it does not fit the evidence now. The article’s hypothesis still holds at this time and, if correct, means that clinicians are erroneously continuing to tell patients with seroma-only BIA-ALCL they have ‘cancer’ when in fact they do not.

Further, such reappraisal of the nature of BIA-ALCL may cause the WHO to review its provisional classification of BIA-ALCL as *always* being a malignant lymphoma and potentially reclassify the disease along the lines of the LyP/pcALCL spectrum. This would have a direct positive consequence for women with non-invasive BIA-ALCL who would not then be given the life-changing diagnosis of ‘cancer’. It would also assist regulators when making decisions about whether to continue to allow surgeons and their patients access to those implants which have proven benefits over smooth implants.

## Compliance with Ethical Standards

**Conflict of interest** All authors declare that they have no conflict of interest.

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