

Case Report

A Further Case Report from the United Kingdom of Breast Implant Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) and a Reason to Avoid the Subpectoral Plane

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Abstract: Breast Augmentation is only second to liposuction as the most commonly performed Aesthetic Surgery procedure in the United Kingdom with a “guestimated” 50,000 cases per annum. Silicone elastomer shells containing silicone gel implants have been used continuously for over 50 years in the UK. Recently Anaplastic Large Cell Lymphoma (BIA-ALCL) has been associated in women having breast implants with variants of a disease process that may remain intracapsular and resolved by removal of implant and total capsulectomy, or nodular and metastatic with proven risk of mortality. An MHRA ‘advisory notice’ merely confirms the views of the MHRA that breast augmentation is safe, nothing needs to be done for existing augmented patients and even if a women develops this condition it can be successfully treated. However there have been nine deaths from BIA-ALCL and actually what Surgeons urgently need is advice on best management protocol and encouragement for international collaboration and evidence based medicine. Diagnosis of BIA-ALCL is dependent upon awareness, correct diagnostic immune staining techniques and review by knowledgeable histopathologists. Recommendations on management of BIA-ALCL should follow the guidelines of Kim et al in 2015. It is important to collect data and outcomes on such patients. The use of submuscular plane for primary breast augmentation should be carefully reconsidered in ensuring safe and complete capsulectomy in the event of BIA-ALCL.

Keywords: Breast Augmentation, Silicone, Breast Implant, Anaplastic Large Cell Lymphoma

1. Introduction

As a conservative estimate there are between 5 and 10 million women globally with silicone gel breast implants. The actual figures are likely to be in excess of 20 million women considering that about 300,000 implants are inserted annually in South America and according to the 2015 Procedural Statistics report from ASAPS 305,856 breast augmentations were carried out in 2015 which have suggested to some that since the first implants were inserted in 1962, approximately 4% of women in the USA have implants that have been used for cosmetic and cancer reconstruction. In addition about 30%

of women, for all reasons have their implants exchanged within 10 years of augmentation [1].

In the United Kingdom there are no accurate figures but breast augmentation is the most common cosmetic surgical procedure and the best guestimate suggests about 50,000 cosmetic breast augmentations per year. This is partly based on non-validated data published in the media by the British Association of Aesthetic Plastic Surgeons (BAAPS), whose members performed approximately 10,000 augmentations in 2012 [2]. However, a larger group of Plastic Surgeons that are members of the mainstream British Association of Plastic Reconstructive and Aesthetic Surgeons (BAPRAS) and the exclusive UK

Association of Aesthetic Plastic Surgeons (UKAAPS) probably do more but there are no figures. There is also an expanding group of Breast Surgeons probably doing as many implant augmentations as the Plastic Surgeons, however the UK 'groups' that advertise probably perform at least double the number of breast augmentations than BAPRAS, BAAPS and UKAAPS member surgeons added together. With international calls for the introduction of a global implant registry the collation of meaningful data could become a real possibility.

Plastic Surgeons from all over the world have been inserting silicone elastomer and gel filled breast implants since Cronin and Gerow implanted the first American women, Tammi Jean Lindsey, in 1962. The history thereafter is beautifully described in an article by Ewan Mac Askillin in 'The Guardian' newspaper in 2012 [3] and this has complimented scientific articles, including by Maxwell et al [4] in an article discussing the development of silicone implants. Since the early days of implantation there have been scares on safety including risk of breast cancer but these have proven ill founded and indeed there has never been a publication within a peer reviewed journal to indicate any relationship [5].

From their outset the commonest problems associated with silicone implants has been capsular contracture related to gel bleeding, biofilm, haematoma or other inflammatory aetiology. Implant shell coverings and gel consistency were altered by manufacturers in an attempt to address these issues. Interestingly all of the major manufacturing companies based in the USA used medical grade silicone sourced from only two major providers from within the USA.

By 1992 additional concerns had been raised with silicone gel implants, especially autoimmune disease, arthritis, tiredness, lethargy, depressive illness and symptoms similar to ME. Symptomatic patients were heavily backed and supported by powerful lobby groups mainly working alongside the regulatory Food and Drugs Administration (FDA) in the USA. By this time virtually all of the major breast implant producers were American but safety data was so unreliable that the resultant FDA moratorium in 1992 [6] weeded out all but two major producers who then proceeded to supply virtually all of the worlds implants over subsequent years. Within the USA saline filled implants became the most popular breast implants and were produced by the same companies, but over a decade later and after extended clinical studies, the manufacturing duopoly finally went on to regain approval to sell their silicone gel filled products (now manufactured offshore) in the USA. The FDA accepted the 8 and 10 year safety profiles provided by the manufactures, but they also acknowledged the deficiencies, confounders and inaccuracies within the data with neither company able to compare like for like figures and a poor patient compliance to follow up. These two implant manufacturers were producing, marketing and selling cohesive gel round and anatomical implants to the rest of the world from the early 1990's, especially during the FDA imposed moratorium in the USA. These now more cohesive gel implants were designed by USA Surgeons working alongside the manufacturers as consultants in the 1990's and they travelled the world supporting the use of these implants

that they as American Surgeons had limited access because of the FDA moratorium. Subsequently European Surgeons gained 15 years of comprehensive experience with anatomical and round, more cohesive, silicone gel implants before their American counterparts. There are problems with anatomical silicone textured implants that USA surgeons and patients will discover over time.

In the USA the preference until the mid 2000's, by necessity, was for saline implants and the main concerns appeared to be whether smooth or textured implants had a lower capsular contracture rate. USA Surgeons did not have general access to anatomical implants until 2012 and even then the first anatomical implants approved by the FDA were manufactured in Brazil. Other European breast implant manufacturing companies spawned, including the French company making the now infamous PIP prosthesis. To the credit of the FDA they did not approve the sale of this implant in the USA. Unfortunately the United Kingdom's regulatory body, the MHRA, through its CE mark, had permitted the sale and subsequent use of many thousands of PIP implants. There are now only three breast implant manufacturers with FDA approval to sell in the USA. None of the European manufacturers with CE Mark approval to sell in Europe have FDA approval to sell in the USA because they cannot provide adequate safety profile data on their implants.

The PIP scandal exposed the most recent immunological concerns of a possible relationship of silicone breast implants with Anaplastic Large Cell Lymphoma (ALCL) in 2012. The UK and other international regulatory bodies were castigated in the media because of their delay in response to concerns of potential dangers from the use of non-medical grade silicone, but the scandal came to a head when a patient with these implants died from ALCL. ALCL associated with silicone implants (BIA-ALCL) is not however a recent discovery and may also occur in the absence of implants (7). The condition can occur in patients with saline implants but no implant type or style appears exempt. The fact that the majority of reported cases have occurred in the USA with textured shells made via salt extraction technology is a little strange given that the condition appears before and around the tenth year after implantation. The USA has only been allowed to use silicone gel filled implants since 2005. However BIA-ALCL has occurred in a significant number of women with saline filled implants and during the FDA moratorium these were the only permitted prostheses available in the USA, unless the patients were part of FDA approved extended clinical studies. BIA-ALCL was not however apparent during these studies. One would consider the two FDA approved manufacturers to actually have a larger cohort of ALCL patients within Europe and the rest of the world if it were a problem associated with the silicone cohesive gel. This in fact is not the case, but if it is accepted that the presentation of 'Acute Swelling Syndrome' occurs in approximately 1:100,000 women with implants and that 1:100,000 of these are ALCL, we expect a relative risk of ALCL in about 1:1million implanted patients (McGhan presentation to the American Society of Plastic Surgeons, ASPS -2012), which is a very rare association. It is more likely

associated with the outer casement acting as a foreign body triggering an abnormal lymphoid response.

According to Brodie et al in 2015, there have only been seventy-nine reported ALCL cases in the world literature, but they identified a further 94 non-reported cases worldwide which they believe are BIA-ALCL. These cannot be substantiated. There have also been nine deaths from BIA-ALCL according to Brodie et al. in their publication (8). Rupani et al in 2015 also extensively reviewed the literature and found only 71 confirmed cases of BIA-ALCL amongst other marrow derived tumours in breast [7]. There have been 2 other reported cases in the UK over the past year [9, 10]. Accepting this is a rare tumour, either ALCL does appear more commonly in the USA, or the rest of the world, have not been identifying or investigating cases as thoroughly and are consequently under-reporting.

The tumour can be a diagnostic challenge given that the condition is caused by a little understood malignant transformation of the 'T-Cell Lymphocyte' and may present with different natural histories from a relatively benign intracapsular ALCL causing seroma, to aggressively malignant nodules or lymphadenopathy which can lead to death [11]. It is possible that the malignant transformation of lymphocytes has an implant associated, microbial induced, chronic antigenic stimulation aetiology [12]. It is also possible that there is a subset where the condition is missed and disappears. This may be the case when some implants are coincidentally removed for other reasons including lifestyle or problems. To detect this condition aspirated lymphoid tissue within seroma from around the implant characteristically stains as CD 30 positive and Anaplastic Lymphoma Kinase (ALK-1) negative. These special immune stains and others [13] are not routinely requested or used by histopathologists on excised breast capsules, or on fluid aspirates. These have to be specifically requested and interpreted and this therefore may be a reason for variable detection rates between countries.

Although the Medicines and Healthcare products Regulatory Agency (MHRA) has sent out a medical devices alert in 2014 about the possible association between silicone implants and ALCL they neither advise to remove implants nor to cease implanting women requesting augmentation for cosmetic reasons. Only one UK case had been previously reported in the literature and this was not in a cosmetic augmentation patient [14]. Nevertheless the MHRA 'advisory notice' merely confirms the views of the MHRA that breast augmentation is safe, nothing needs to be done for existing augmented patients and even if a woman develops this condition it can be successfully treated. However as we know there have been nine deaths from BIA-ALCL and actually what Surgeons urgently need is advice on best management protocol and encouragement for international collaboration and evidence based medicine. The purpose of this case report is to add to the increasing literature on the subject and help formulate a standard protocol for management.

2. Case Report

A 47 year old woman (LB) with bilateral breast implants presented with a sudden swelling of the right breast in January 2016. The original breast augmentation was in August 2003 and 300g x 2 Style 120 Mc Ghan (Allergan/Mc Ghan, USA) implants were positioned in subpectoral planes. During follow up consultation in 2004 there was a small asymptomatic palpable ridge noted on the right implant and in 2005 there was a small fold on the right implant and lateral displacement indicating mobility. She wanted larger breasts and was advised to change the Mc Ghan for Silimed polyurethane implants (Silimed, Brazil) but she was lost to follow up and in fact did not proceed to the exchange procedure.

There was no obvious causation of the swelling and no apparent problem with the implants on ultrasound. The effusion was aspirated on two separate occasions (500mls total) under ultrasound control. Each sample was analysed by two separate histopathologists but interestingly it was only after a third pathologist used CD30 and ALK immunostains that a positive diagnosis of BIA-ALCL could be made (figs 1, 2).

After a general screening process the patient had removal of both implants and right total capsulectomy in March 2016 (fig 3). Using an 8 cm submammary incision the right breast capsule was removed intact containing an 82 ml effusion (fig 4). The capsule was easily dissected from surrounding tissues and was only adherent medially over the lower costochondral junction. The resultant space was approximated with quilting sutures and a drain was removed after 24 hours.

Opening the capsule revealed a slightly folded intact 300 g McGhan Style 120 implant covered in debris (fig 5). The capsule was palpably smooth with no nodularity or extracapsular mass. The effusion contained small, fibrous, free floating plaques which were also analysed. Histology confirmed BIA-ALCL with no extracapsular extensions but tumour cells were present within adherent fibrinous plaque on the inner surface of a section of the capsule (fig. 6, 7, 8, 9).

No adjunct treatment has been recommended but there is no evidence of early recurrence and she will undergo regular screening and long term follow up.

Histology

Extensive immunohistochemical studies were undertaken on effusion aspirate samples and capsular histology. Table 1 shows the results.

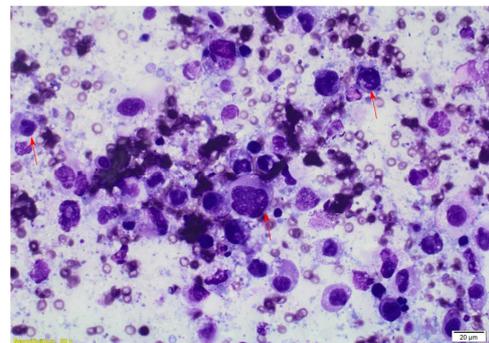


Fig. 1. HP. Cytology of effusion aspirate from right breast showing atypical lymphoid cells (examples arrowed) with embryo shaped nuclei.

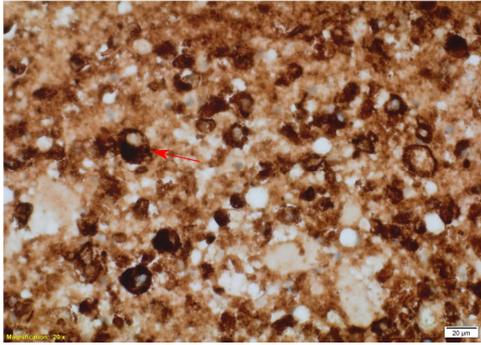


Fig. 2. CD30 immunohistochemical staining of cell block preparation from breast effusion aspirate. The brown stained atypical lymphoid cells (examples arrowed) are CD30 positive -suggestive of BIA-ALCL.

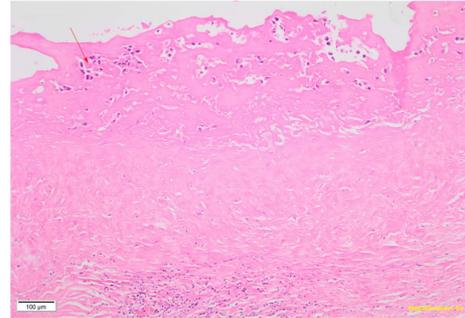


Fig. 6. LP, H and E stain of breast capsule showing atypical lymphoid cells within a fibrin plaque (arrowed). This corresponds with the contact point between the McGhan elastomer implant and the tissues.



Fig. 3. The 47 year old patient (LB) supine on operating table immediately preoperatively showing swollen right breast even after the recent aspiration of 500mls clear effusion fluid.

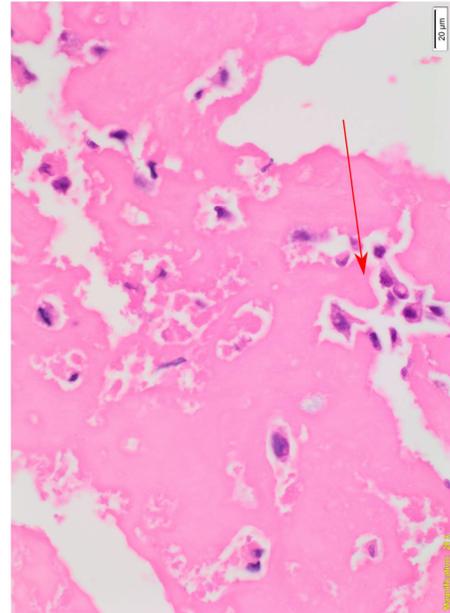


Fig. 7. HP, H and E stain of breast capsule showing atypical lymphoid cells within fibrin plaque adherent on the inner surface of the capsule (arrowed).

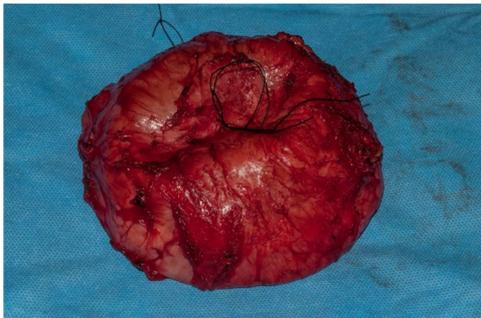


Fig. 4. Total capsulectomy specimen containing a non-adherent, intact, 300ml McGhan breast implant.

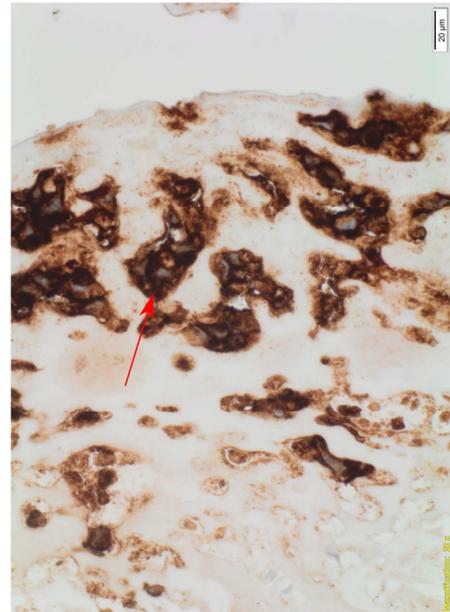


Fig. 8. CD30 Positive stain on atypical lymphoid cells adherent within a fibrinous plaque on the inner surface of the breast implant capsule (arrowed).

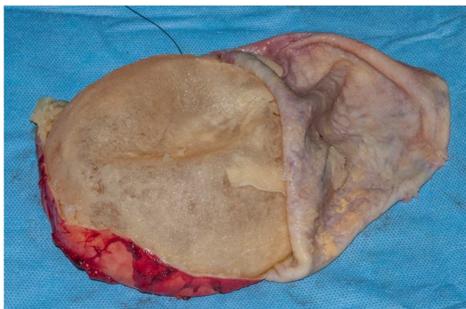


Fig. 5. An anterior flap of capsule has been surgically reflected and the implant removed to show the internal appearance of the autologous capsular tissue. This is the surface in contact with the non-adherent implant and is covered with a creamy deposit. The capsule itself is about 3mm thick. There were no palpable nodules but fibrinous deposits and free floating smooth fibrous plaques were seen.

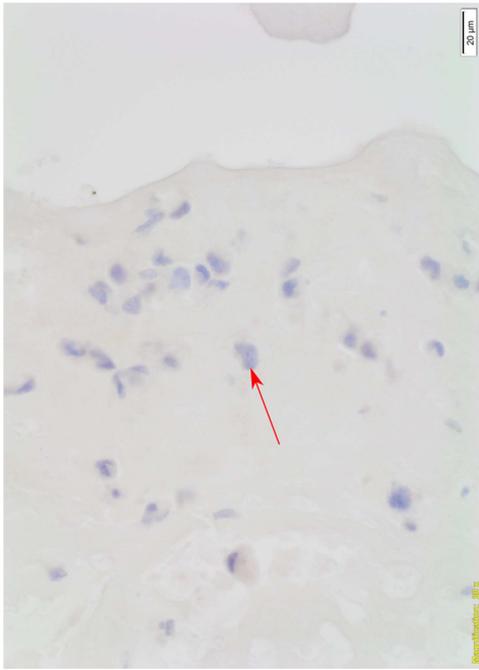


Fig. 9. ALK1 surface antigen stain Negative on fibrinous intracapsular atypical lymphoid cells, confirming BIA-ALCL. Example of ALK 1 negative cell arrowed.

3. Discussion

Over the course of the last 26 years over 4000 women, including this patient have had a variety of FDA approved silicone implants inserted by the senior author (JF). These were mainly indicated for cosmetic reasons but also for post-mastectomy, congenital deformity and asymmetry reconstructions within both the private sector and National Health Service (NHS) in the United Kingdom. This is the first case of BIA-ALCL within this large series presenting at the Breast Surgery Unit at Mid Essex Hospitals. The diagnosis was based upon repeated cytology aspirates demonstrating CD30 Positive and Alk-1 Negative Immunohistochemistry and eventually confirmed by Immunohistochemistry on the excised capsule.

Since ALCL was first reported by Keech et al in 1997 [15] in a patient with a saline tissue expander breast reconstruction, BIA-ALCL has been sporadically reported as a rare but definite clinical entity within isolated single case reports and small series of cosmetic breast augmentation. In 2015 Rupani et al [7] comprehensively searched the literature and distinguished between BIA-ALCL and other forms of lymphoma. The disease may occur in women with either saline or silicone implants. Interestingly there have been reports in the Orthopaedic literature of similar findings in patients following arthroplasty and metal on metal implants are now being replaced because of a recently demonstrated association with aseptic, lymphocyte-dominated vasculitis-associated lesion (ALVAL). There had been no firm recommendations on the management of BIA-ALCL until recently because of lack of large series studies and evidence based data.

More recently however, Kim et al in 2015 [16, 17] comprehensively investigated and published the

recommendations that were decided by an interdisciplinary panel of experts from leading centres within the USA. The recommendations of the panel are:-

- (1) This disease should be called "BIA-ALCL"
- (2) Late 'seromas' occurring >1 year after breast implantation should be evaluated via ultrasound, and if a 'seroma' is present, the fluid should be aspirated and sent for culture, cytology, flow cytometry [18] and cell block to an experienced hematopathologist.
- (3) Surgical removal of the affected implant and capsule (as completely as possible) should occur, which is sufficient to eradicate capsule-confined BIA-ALCL.
- (4) Surveillance should consist of clinical follow-up at least every 6 months for at least 5 years and breast ultrasound yearly for at least 2 years.
- (5) BIA-ALCL is generally a biologically indolent disease with a good prognosis, unless it extends beyond the capsule and/or presents as a mass. The committee firmly disagreed with statements from others that chemotherapy and radiation therapy should be given to all patients with BIA-ALCL.

In the light of our recent experience we commend Kim et al's advice on management for all new cases of BIA-ALCL presenting with acute swell syndrome in the absence of mass. From the available evidence and contrary to the updated advice from the FDA (2016) we agree with others that there is enough evidence that this is a variably malignant condition that is cured by surgical removal of the stimulus for the aberrant T-Cell lymphocyte production [19, 20, 21] and complete capsulectomy is recommended in all cases.

It is important for Plastic Surgeons to reconsider the tissue plane they use for primary augmentation. In hindsight it is prudent to use sub-fascial or sub-mammary planes rather than sub-pectoral planes for augmentation wherever possible, simply because of comparative ease and likelihood of total capsulectomy. It is significantly harder to guarantee full and safe capsular excision if the implants have been inserted in sub-muscular or dual planes. In cases of acute swelling there is usually no adherence of the capsule to the implant elastomer, resulting in a much larger space than the implant occupies. There may be hypergranulating tissue on costal cartilages which is never present when implants are in extra-pectoral pockets. The adherent capsule cannot be removed in its entirety without major risk if stuck to the cartilage or if adherent and high in the axilla. Historically implants were inserted in the sub-muscular plane to hide prominent upper poles and rippling as the implants encapsulated and also with the presumption that overlying muscular activity would reduce the incidence of capsular contracture around the implant. In fact capsular contracture still occurs in up to 20% of cases at 10 years and if implants are exchanged the incidence of recurrent capsular contracture is significantly increased.

Both preventing capsular contracture and reducing any implant surface stimulus to T lymphocyte activation and clonal transformation should be the main objectives for the next generation of implants and surgeons. It is vitally important that data is collated and sound advice is given to all

implanting clinicians. Informed consent necessitates the requirement of Surgeons to inform potential patients of these risks, however small.

4. Conclusion

BIA-ALCL is a real entity and as more cases are being discovered we are more likely to see the true incidence of this condition. Up until recently this condition had not been associated with silicone breast implants in the United Kingdom. Indeed the considering the numbers of breast implants inserted over the past 40 years the incidence is extremely rare. It may be though that under-diagnosis and under-reporting can be attributed to lack of awareness from both Surgeons and Histopathologists. From the technical point of view most Surgeons insert implants into submuscular or dual plane pockets. With the need for total capsulectomy and no tumour spill in the event of BIA-ALCL, Surgeons must consider this as the appropriate plane of pocket dissection because ensuring total capsulectomy from a subpectoral pocket is extremely difficult. There are clearly indications for submuscular placement of silicone implants especially where there is almost complete lack of breast tissue, but in most cases implants can be adequately covered by soft tissues and it is up to manufacturers and Surgeons to work out how to reduce capsular contracture with more certainty.

Table 1. Analysis of effusion aspirate and capsule tissue.

Seroma	Capsule
ALK1 Negative	ALK1 Negative
CD3 Negative	CD3 Negative
CD4 Positive	CD4 Positive
CD8 Negative	CD8 Negative
CD30 Positive	CD30 Positive
CD68 Negative	CD68 Negative
EMA Positive	EMA Positive

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