

**Breast Implant Associated Anaplastic Large Cell Lymphoma: The UK experience.**  
**Recommendations on its management and implications for informed consent.**

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## **Abstract**

### **Background**

Breast implant-associated anaplastic large-cell lymphoma (BIA-ALCL) is a rare, Non-Hodgkin lymphoma arising in the capsule of breast implants. BIA-ALCL presents as a recurrent effusion and/or mass. Tumours exhibit CD30 expression and are negative for anaplastic lymphoma kinase (ALK). We report the multi-disciplinary management of the UK series and how the stage of disease may be used to stratify treatment.

### **Methods**

Between 2012 and 2016, 23 cases of BIA-ALCL were diagnosed in 15 regional centres throughout the UK. Data on breast implant surgeries, clinical features, treatment and follow-up were available for 18 patients.

### **Results**

The mean lead-time from initial implant insertion to diagnosis was 10 years (range: 3-16). All cases were observed in patients with textured breast implants or expanders. Fifteen patients with breast implants presented with stage I disease (capsule confined), and were treated with implant removal and capsulectomy. One patient received adjuvant chest-wall radiotherapy. Three patients presented with extra-capsular masses (stage IIA). In addition to explantation, capsulectomy and excision of the mass, all patients received neo-/adjuvant chemotherapy with CHOP as first line. One patient progressed on CHOP but achieved pathological complete response (pCR) with Brentuximab Vedotin. After a mean follow-up of 23 months (range: 1-56) all patients reported here remain disease-free.

### **Discussion**

BIA-ALCL is a rare neoplasm with a good prognosis. Our data support the recommendation that stage I disease be managed with surgery alone. Adjuvant chemotherapy may be required for more invasive disease and our experience has shown the efficacy of Brentuximab as a second line treatment.

### **Keywords:**

Breast implant associated anaplastic large cell lymphoma (BIA-ALCL)  
Breast implant effusion

## **Introduction**

Breast implant associated anaplastic large cell lymphoma (BIA-ALCL) is an extremely rare, Non-Hodgkin lymphoma of T-cell origin. This association was highlighted by the Food and Drug Administration in the United States in 2011 (1, 2) and, whilst breast implants have been in use since 1962, the first case was only reported in 1997 (3). Since then, whether through increased use of implants, or growing clinician awareness and acceptance of this rare complication, the rate of diagnosis is rising: the largest published case series reports 173 cases (4, 5). De Jong and colleagues estimate an incidence of BIA-ALCL of 1-3 cases in 1 million breast implant cases per year (6) however opinion in some other countries express possible higher risks (7) and more robust epidemiological studies are required.

The aetiology of this disease remains unclear and, despite the growing body of evidence implicating chronic inflammation within the capsular biofilm, some authors advise caution in drawing conclusions until science catches up with this unusual entity (8, 9). In the modern era of breast augmentation and reconstruction the proportion of textured implants used greatly exceeds the number of smooth shell devices and this may partly explain why almost all cases have arisen in association with textured implants. It is not clear if this is the whole story and one working theory is that, when compared with smooth implants, concavities present from the macro-texturing process predispose to sub-clinical infection and/or to chronic inflammatory stimulation (10). Honghua et al have recently reported an increased prevalence of certain gram-negative organisms (*Ralstonia* spp) within the microbiome of implant capsules taken from patients with BIA-ALCL compared to controls. The notion that a pro-inflammatory environment can precede cancerous change is not a new one; the very rare association of *Helicobacter pylori* infection and gastric lymphoma is already well documented (11, 12).

## **Presentation of the disease**

Women who develop BIA-ALCL typically present with either large volume peri-implant effusions (80%) or solid capsule-related masses (20%)(13). Many benign causes for the sudden development of fluid around the implant exist and these will vastly outnumber those due to BIA-ALCL (14) . Diagnosis is made by the finding of abnormal cells in the aspirate or biopsy accompanied by the hallmark uniform over-expression of CD30 and negative staining for Anaplastic Lymphoma Kinase (ALK) (5, 15-17).

As proposed by Clemens et al, stage I disease remains confined to the effusion or a layer on the luminal side of the capsule, whereas stage II (and above) disease presents with extra-capsular spread, regional nodal or distant metastases (18). Whether these two presentations are indeed distinct disease entities or whether they are at opposing ends of a disease spectrum remains unknown at present. Patients with stage I disease can be treated adequately with implant removal and total capsulectomy. These patients may be at risk of over-treatment with adjuvant medical therapies if the indolent natural history of this disease is not fully appreciated.

In patients with stage II disease (locally advanced) and stage III/IV disease (regional and distant spread), treatment may involve adjuvant therapies. Standard chemotherapy regimens used in the management of systemic ALCL are anthracycline-based, such as cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP). Such regimens appear to be more effective in patients with ALK-positive systemic ALCL when compared to ALK-negative disease (5-year survival rates of 70-90% Vs. 40-60%). In patients with ALK negative systemic disease CHOP may be ineffective. Other regimens may be used and remissions consolidated with autologous stem cell transplantation (19). In BIA-ALCL (characteristically ALK-negative on immunohistochemistry), CHOP regimens have been reported for adjuvant treatment – however, their efficacy remains to be proven in the first line. In six reported cases of death secondary to BIA-ALCL, two thirds of patients receiving CHOP progressed through treatment (18). Clinical trials assessing the use of Brentuximab Vedotin, a monoclonal anti-CD30 antibody conjugated to the anti-microtubule agent monomethyl auristatin E, for the treatment of relapsed, refractory ALCL may have a specific role in ALK-negative systemic disease and BIA-ALCL. Trials have reported response rates of 86% and complete remission rates of 59% in ALK-negative tumours (20, 21). Brentuximab Vedotin appears to be well tolerated and patient-reported outcomes appear to show significant improvements in quality of life after commencing this therapy compared to other agents (22). It is noteworthy that none of the six reported patients that died from BIA-ALCL received Brentuximab Vedotin (18) but if a similar response is seen in BIA-ALCL, it may herald a paradigm shift in the treatment of advanced BIA-ALCL.

It is mandatory that all confirmed cases in the United Kingdom are reported to the MHRA (Medicines and Healthcare Products Regulatory Agency), or the equivalent medical regulatory

authority if outside. The Plastic Surgery Foundation, based in the United States of America, in collaboration with the American Society of Plastic Surgeons (ASPS) and the Food and Drug Administration (FDA), have created a BIA-ALCL-specific database for collecting and following up all cases of BIA-ALCL worldwide and after patient consent we strongly recommend confirmed cases be included in this registry (23). The PROFILE registry also provides up to date information on BIA-ALCL.

## **Patients and Methods**

In total, 23 cases of BIA-ALCL have been diagnosed and within the UK to date. Through close collaboration between the Association of Breast Surgery (ABS), British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS) and the British Association of Aesthetic Plastic Surgeons (BAAPS) networks we gathered information about cases of BIA-ALCL within the UK population. We report a case series of 18 patients diagnosed with BIA-ALCL between 2012 and 2016 across 15 regional centres. One of the patients has already been presented as a case report in the literature (24) and an earlier summary of UK cases diagnosed to date was presented at the San Antonio Breast Cancer Conference 2016 (25). Table 1 summarises the details of each case.

## Results

The mean age at diagnosis was 52 years (range 29-73 years) and the mean lead-time from implant placement to diagnosis was 10 years (range 3-16 years). Indications for implant use were breast augmentation (56%), breast reconstruction following mastectomy for breast cancer (33%) and reconstruction following mastectomy for risk reduction (11%). Seven patients who presented with a recurrent, large-volume effusion were diagnosed with BIA-ALCL between 1 and 3 years after their initial symptomatic presentation with effusion. Six of the seven patients had capsule-confined disease (stage I) at eventual diagnosis. In two of these cases, a retrospective review of the earlier cytopathology from previous symptomatic presentations suggested the presence of BIA-ALCL in previous aspiration samples. They came to no harm and remain well and disease-free. One patient, who is discussed in more detail later, appeared to have seeding of BIA-ALCL from the capsule to the site of the surgical drain after capsulectomy and implant exchange for a problematic effusion not thought to be secondary to BIA-ALCL at the time of surgery.

Ten patients had the diagnosis of BIA-ALCL made pre-operatively. This was accomplished by fine needle aspiration (FNA) of effusion fluid (N=5), needle core biopsy (NCB) of the presenting mass (N=3), capsule biopsy alone (N=1) and, in one case, a combination of capsule biopsy and FNAC was required. Three patients had the diagnosis made following surgery: one patient had a capsulectomy and implant replacement with a micro polyurethane textured device for recurrent effusion; one had exchange of implant and seroma drainage for change in shape for an assumed ruptured implant (which was intact at surgery), the other was diagnosed following review of cytology from the drained effusion.

## **Stage I disease**

All patients were managed through a multidisciplinary team with specialist haemato-oncology opinion. Using current BIA-ALCL staging, 15 patients had Stage I disease and presented with a recurrent, large volume effusion. They were treated successfully with implant removal and total capsulectomy and have a mean follow up of 21 months to February 2017. The indications for implant insertion were: bilateral breast augmentation (BBA) (N=7), bilateral risk-reducing mastectomy (RRM) with immediate breast reconstruction (N=2), mastectomy for cancer with immediate breast reconstruction (N=4) and mastectomy with delayed breast reconstruction (N=2). Of this latter group, one patient was reconstructed using tissue expansion and the second underwent implant assisted Latissimus Dorsi (LD) flap reconstruction. Two patients with stage I disease had received prior breast cancer related adjuvant chemotherapy, chest wall radiotherapy and endocrine therapy with Tamoxifen.

Seven patients diagnosed with BIA-ALCL still had their initial implants in situ at the time of diagnosis of BIA-ALCL. Of the remainder, six had undergone tissue expander (TE) insertion at primary reconstruction of which five had undergone exchange for a fixed-volume implant and one had undergone exchange to an identical tissue expander prior to developing BIA-ALCL. The remaining two patients had previous fixed volume implants exchanged for replacement implants on at least one occasion prior to diagnosis of BIA-ALCL.

In total, eight patients had at least one other device implanted before the current in situ device. The details of the device was unknown in one patient.



## **Stage II disease**

Three patients presented with stage IIA disease. One patient, who had undergone previous BBA with subsequent exchange of implants and capsulectomies, presented with a mass two months following surgery and had BIA-ALCL confirmed on biopsy. She was entered into the ECHELON 2 trial (CHOP v. Brentuximab Vedotin + CHOP). Her treatment remains blinded within the confines of the trial – however, she achieved a complete clinical and radiological (PET-CT) response and was treated with further adjuvant radiotherapy to her chest wall.

The second patient with stage II disease had previously undergone BBA with subsequent implant exchange and bilateral capsulectomies (performed overseas four months prior to presentation) and then developed a mass at the surgical drain site. Biopsy of the mass confirmed BIA-ALCL. We postulate this represents cutaneous seeding to the drain site from undiagnosed BIA-ALCL at the time of implant exchange and strengthens the argument for complete en bloc capsulectomy with the implant. Unfortunately, there is no capsule available for retrospective pathological examination in this case. She underwent wide local excision of this mass with adjuvant CHOP chemotherapy and radiotherapy and to date, remains well with no evidence of recurrence at 4 years post-treatment.

The third patient with stage II disease had previously undergone BBA and presented with an isolated mass adjacent to the implant on the anterior chest wall, which was confirmed as BIA-ALCL on biopsy. She underwent three cycles of CHOP chemotherapy and progressed rapidly during treatment to develop life threatening chest wall/thoracic cavity involvement (figure 2 a and c). It was unclear whether resection would be feasible, so a trial of neoadjuvant Brentuximab Vedotin was commenced. She achieved complete clinical and radiological response following six cycles (figure 2 b-e) and underwent bilateral total capsulectomy and implant removal, which confirmed a pathological complete response (pCR).

All patients have been followed-up to date with PET-CT and all remain disease free with the treatment as discussed.

## Discussion

We show that BIA-ALCL is a diagnosed entity in the UK with 44% of patients having implants for reconstruction and the remainder having primary breast augmentation (56%). This differs only marginally from the previous published series when 60% of cases of ALCL were seen following BBA and the remaining 40% seen in reconstruction patients (5). More importantly there does not appear to be clustering of cases to a specific surgeon or unit or geographical location suggesting that local factors do not affect the development of BIA-ALCL.

Delays in diagnosis in seven (39%) patients in this series are probably due to the lack of awareness of BIA-ALCL in women, breast radiologists, pathologist, breast and plastic surgeons. Work has started to raise awareness amongst women (26) and UK professionals alike (27, 28).

Systemic ALCL (non-BIA associated) is a rare and aggressive lymphoma with poor outcomes requiring extensive systemic treatment and is traditionally staged using the Ann Arbour classification which may risk over-staging and thus over-treating the more localised BIA-ALCL. The newer BIA-ALCL specific staging system proposed by Clemens et al recognises a very low risk group with localised intra-luminal disease and a separate higher risk group with extra-luminal disease or a breast mass who will benefit from more aggressive systemic treatment (29). The UK data support this classification.

Stage I BIA-ALCL presenting as a sudden, late effusion is on the whole an indolent disease. Seven patients in this series had symptomatic effusions some time prior to final diagnosis of BIA-ALCL and six but did not have disease progression during that time. One patient in whom there was a delay in diagnosis appeared to progress by seeding of cells following implant exchange into adjacent normal tissue (thus up-staging the disease). This highlights the importance of complete capsulectomy with en bloc excision of the capsule and effusion during surgery if BIA-ALCL is either already diagnosed or clinically suspected.

Stage II BIA-ALCL presents as either an extra-capsular mass (T4M0N0) or has lymphoma cells infiltrating the capsule with nodal metastasis (T1-3N1M0) and appears to behave in a more aggressive manner. Our experiences in managing such stage II BIA-ALCL cases resonate with global opinion that these patients appear to benefit the most from adjuvant therapies. Specifically, in our series, we report for the first time the use of Brentuximab Vedotin in the neoadjuvant setting for BIA-ALCL in a patient who progressed on first line CHOP. She demonstrated a complete clinical, radiological and pathological response (figure 2). Whilst it is not possible to speculate on the details of randomisation for the patient entered into ECHELON 2, we look forward to the maturation of this trial data as they may change the current standard of care for ALK-negative ALCL – and BIA-ALCL in particular – significantly.

In addition, the risk of developing recurrent, or a new primary, BIA-ALCL tumour if the affected textured implant is exchanged with a new device remains uncertain. Whether the textured implant should be replaced with another textured device, or perhaps a smooth one, also remains unclear. Pragmatically speaking, removing the ipsilateral implant alone in a patient with bilateral implants will result in profound asymmetry, so decisions regarding immediate bilateral implant replacement or bilateral implant removal to maintain symmetry is for discussion between the surgeon and the patient and should be judged on a case-by-case basis however oncological safety should always come before aesthetic considerations. A consensus group consulted on these questions were unable to reach a conclusion due to the dearth of clinical and biological information about this disease (30).

The National Comprehensive Cancer Network in the United States has developed an algorithm for the management of BIA-ALCL (33). Healthcare provision and funding differs in the UK so we propose a modified algorithm for the management of suspected BIA-ALCL specific for the UK health system outlining the requirements for a histological diagnosis and the principles of management (figure 3).

BIA-ALCL is a rare condition that presents with a sudden onset effusion around an implant; it is usually curable by total capsulectomy. Our paper describing the current UK case reports, management and outcomes is part of a wider strategy to raise awareness through education and better information. It is recommended that cases are managed in specialist tertiary centres which have the appropriate experience and expertise in the management of BIA-ALCL. We feel that this will permit consolidation of clinical and research resources and will lead to a better understanding of lymphomagenesis in this context.

### **BIA-ALCL and the breast implant registry**

We can only get more complete data prospectively through national observational studies and BIA-ALCL highlights the relevance and importance of the recently launched Breast and Cosmetic Implant Registry (BCIR) and consenting all patients for inclusion in the registry (31). This national database will help in building up an accurate picture on implant usage and the consequent monitoring and collation of long-term sequelae.

### **BIA-ALCL and consent**

One of the broader issues related to BIA-ALCL pertains to patient consent. The occurrence of BIA-ALCL highlights the importance of surgeons consenting patients for inclusion in the implant registry (31). A recent, informal conference poll of plastic surgeons in the UK suggested that 75% of respondents did not routinely discuss BIA-ALCL with their patients prior to implant surgery (29). The reasoning for this is unclear – but is likely to stem from a lack of information about, and appreciation of, the disease entity by the surgical world. We can be reassured that the discussion of BIA-ALCL with patients preparing for implant surgery appears to have no deleterious effect on the treatment plan, as patients still undergo implant surgery after being fully informed (29).

Following the recent Montgomery ruling in 2015 in the UK (32), the GMC's Guide to Good Medical Practice (which favours a patient-centred approach to consent) is no longer considered a guide, but is now a mandatory requirement. This stance must be reflected in our decision to discuss BIA-ALCL with patients.

In response to the High Court Judgement in the case of Montgomery 'v' Lanarkshire Health Board, the GMC stated that "risk shouldn't be a numbers game, it should be part of dialogue". "A material risk is one that a reasonable person in the patient's position is likely to apply significance to". In the BIA-ALCL context, although the risk is extremely low, it is nevertheless our duty to inform any patient receiving a breast implant that there is a risk.

The published literature unanimously agrees that BIA-ALCL is a distinct entity and that a failure to inform patients of this risk is a failure in your duty to the patient (18, 29), exposes the surgeon to potential litigation and is significantly at odds with the GMC guidelines on Good Medical Practice.



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Individual case information.

	Lead time to diagnosis from 1st breast implant	Implant indication	Implant used	Presentation	Surgery	Adjuvant treatment	Follow up	Stage
1	16 y	2000: Breast cancer and immediate reconstruction Adjuvant chemo-radio and endocrine therapy	2000 – McGhan saline implant expander 2009 – McGhan 410MM 360 cc	2016 Seroma	Removal of implant Unilateral Capsulectomy	Nil	8 months	I
2	11 y Symptoms at 8 y	2004: RRM and IBR. BRCA 2 carrier	2004 – McGhan 133MV expander 2004 – McGhan 510MX 490 cc 2012 – Allergan Inspira TRF520 2013 – Polytech Polyurethane 495	2012–2015 Recurrent seromas	Bilateral implant removal Bilateral capsulectomy	Nil	14 months	I
3	3 y	2012: BBA	2012 – Allergan MHP 525 cc	2015 Mass chest wall adjacent to implant	Bilateral capsulectomy Bilateral implant removal Unilateral SLNB	Neoadjuvant CHOP progressive disease (3 cycles) Neoadjuvant Brentuximab 6 cycles	10 months	IIA (yp cPR)
4	7 y Symptoms at 6 y	2007: BBA	2007 – Nagor Cogel XA 400 cc	2013–2014 Recurrent seromas	Bilateral implant removal Bilateral capsulectomy	Nil	32 months	I
5	12 y	2002: BBA	2002 – Textured McGhan 340 cc 2014: Nagor IMP-300	2014 Recurrent seroma 2014: Mass	Bilateral implant removal Bilateral capsulectomy	CHOP+ (echelon2 trial) Randomised to CHOP ± Brentuximab (double blinded)	28 months	IIA
6	4 y	2008 RRM and IBR	2008 – Allergan Style 150 expander 2009 – Allergan Style 150 expander	2012 Seroma	Unilateral capsulectomy Bilateral implant removal	Nil	56 months	I
7	16 y	1999: BBA	1999 – McGhan 120 450 cc	2015 Seroma	Bilateral capsulectomy Bilateral implant removal	Nil	20 months	I
8	9 y	2006: BBA	2006 – PIP 2010 – Allergan round textured	2015 Seroma	Bilateral capsulectomy Bilateral implant removal	Nil	15 months	I
9	13 y	2003: BBA	2003 – McGhan 120 300 cc	2016 Recurrent seroma	Bilateral implant removal Ipsilateral capsulectomy	Nil	14 months	I
10	12 y	2002: Mx and IBR contralateral augmentation	2002 – Nagor GFX 240 cc	2014 Seroma	Ipsilateral implant exchange (Mentor CPG332) Ipsilateral capsulectomy Contralateral implant exchange (Nagor GFX)	Nil	30 months	I
11	9 y	2003: BBA	2003 – U/K 2007 – Nagor GFX 340 cc 2012 – exchange of implants and capsulectomy overseas	2012: Mass at surgical drain site	Excision of mass Bilateral capsulectomy at time of Implant exchange overseas (no path)	Adjuvant CHOP chemotherapy Adjuvant radiotherapy (30 Gy in 15#)	56 months	IIA

**Fig 1.**



**Fig 2.**

