

A Case Report of a Node Positive Breast Implant Associated – Anaplastic Large Cell Lymphoma

Mustata L^{1*}, Collins G², Ilie D³, Parulekar V³, Adams R³ and Roy PG⁴

¹Breast Surgery Department, Oxford University Hospitals, UK; Gynecology Dpt. Filantropia Clinical Hospital, Bucharest, Romania

²Oncology Department, Oxford University Hospitals, UK

³Breast Radiology Department, Oxford University Hospitals, UK

⁴Breast Surgery Department, Oxford University Hospitals, UK

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***Corresponding author:** Laura Mustata, Breast Surgery Department, Oxford University Hospitals, UK; Gynecology Dpt. Filantropia Clinical Hospital, Bucharest, Romania, Tel: +40740297218; Email: lauramustata@yahoo.com

Abstract

Background: Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a rare condition associated with breast implants.

Methods: This paper describes a case of node positive breast implant associated ALCL in a young woman who underwent cosmetic breast augmentation 11 years prior to this diagnosis.

Results: She was the first case of BIA-ALCL treated in our institution and emphasizes the importance of multidisciplinary team approach involving breast surgeons, hematologists, pathologists, breast radiologists and radiation oncologists. We have reviewed the available literature in this report. Although most cases of implant associated ALCL can be treated with surgery alone as they are localized, the spread beyond the implant cavity involves discussion about systemic treatment and the sequencing of the various therapies.

Conclusion: Given the prevalence of implants in the community worldwide, it is important to raise awareness amongst medical staff and educate the general population to seek medical attention early.

A unique case report of node positive BIA ALCL

Keywords: Anaplastic Large Cell Lymphoma (BIA-ALCL); Breast Implants; Breast Cancer; Chemotherapy; Breast Surgery

Introduction

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a rare type of T-cell non-Hodgkin lymphoma related to breast implants. 173 cases

have been reported with both reconstructive and cosmetic implants so far [1-3]. The first case of ALCL was reported in 1997 with a textured McGhan saline-filled breast implant (Keech and Creech) presenting as 20mm lesion on the implant capsule. Patient underwent surgery

involving capsulectomy and implant replacement followed by chemotherapy and radiotherapy, ensuring disease free interval for the subsequent years [4].

Although the etiology of BIA-ALCL is not completely elucidated, the possible theories include chronic inflammatory response, immune response, type of implant (smooth or textured), hereditary predisposition or bacteria biofilm. It is obvious that there is an important connection between implants and BIA ALCL regarding the etio-pathogenesis, but questions remain unanswered about this subject [5-7]. One of the plausible causes seems to be the immune response of the T-cells to some antigens in the biofilm of the implant [8]. A study in Australia showed an association between textured implants and an increased number of T cell lymphocytes when compared to smooth surface implants [6,7]. FDA reported 359 cases of BIA ALCL (including 9 deceased) and from 231 that had details about the surface of the implant, over 90% were associated with textured surface of the implants. Of 321 cases that had this information on the type of fill, 186 were silicone gel-filled and 126 were saline filled [8]. 37 reports have been published with 173 cases of BIA ALCL [4]. Some patients diagnosed with BIA ALCL had undergone multiple revisional surgeries and exchange of implants and all had at least one textured implant in their medical history. In 1986 the textured surface implants were available and WHO identified the ALCL in 1985. Probably there are some unrecognized cases before this era [4,9].

Cohort study in New Zealand and Australia showed higher incidence rates, estimated risk was between 1/1000 - 1/10000 in women with textured implants, presuming that only textured implants cause this condition [9-11]. A case-controlled study done in the Netherlands on a population of 9 million women showed an insignificant lower risk (the absolute risk) of developing BIA ALCL in the general population, but for women with breast implants, it was confirmed as 18 times higher. The incidence rate was 1-3 cases/1.000.000 women/year in the latter study. The tendency was higher 10 years post-reconstruction and the mean age at diagnosis was around 50. Nevertheless, some cases of early and late onset have been cited in the literature [12,13]. US study from 2017 showed a rate of incidence of 203 in 100.000.000 persons/year and a 67 times higher rate of BIA ALCL than primary ALCL of breast [14-16].

Most of the patients present with unilateral breast enlargement or new seroma collection near the implant on a localized area, usually more than 10 years after

implant was placed (without any significance when comparing cosmetic versus reconstruction implants) [15-17]. There are a few cases reported to have presented with bilateral symptoms, such as effusion between the implant and the capsule. Often patients complain of breast swelling due to a peri-implant fluid collection, new lump, skin inflammatory changes, capsular contracture (non-specific symptom, 10% of implants), pain, asymmetry [1,17]. Some reported skin lesion as dominant symptom, as papules and some generic clinical features as fever, fatigue, night sweats, axillary lymphadenopathy or other palpable nodes [17].

Guidelines for diagnosis and treatment of BIA ALCL were given by NCCN based on the cases that were reported. BIA ALCL should be suspected in cases of sudden seroma and breast swelling in patients with breast implants, at least one year after their breast surgery, after excluding any breast trauma or infection. Clinical examination should include breasts, axillae, neck and chest wall. If suspicion is raised, further imaging assessment is needed, and ultrasound should be the first approach with fluid aspiration for cytology analysis as gold standard diagnostic method. CT and MRI examination have the same rate of detection as ultrasound, thus ultrasound is the most used method (being cost efficient and accurate). PET CT should be performed to rule out systemic ALCL and for follow up [3,17]. Cytology is used for confirmation of diagnosis and immunohistochemistry analysis together with flow cytometry confirms T cell population, CD30 positive and large anaplastic cells [10].

Ultrasound examination can identify seroma, mass on the implant capsule or mass effect on the surrounding structures or thickened capsule. It is not recommended to routinely perform ultrasound guided aspiration of peri-implant fluid to rule out ALCL; it is only for diagnostic purpose in suspected cases, performed by interventional radiologist or by clinicians using a blunt needle to avoid implant injury and leakage. The analysis of the fluid sample should be performed by a haemato-pathologist and cytology analysis, flow cytometry and immunohistochemistry will show the features regarding ALK, CD30 status and presence or anaplastic cells [1,17].

The differential diagnosis includes primary or recurrent breast cancer, primary breast lymphoma, other forms of ALCL, infection, benign seroma, other breast implant complications [1].

Staging for BIA ALCL is not clearly defined, whether it should follow TNM or Lymphoma guidelines; Ann Arbour system is used as well (early BIA ALCL limited on the breast - IE or limited on the breast and axilla - IIE). Following the natural history of BIA ALCL, this entity seems to metastasize as solid tumors and TNM staging is

more suitable, being also useful for prognosis and oncological treatment [1,3].

The staging is summarized in Table with Classification TNM VS Ann Arbour (TABLE 1).

T - extent of the tumor	N - lymph nodes involvement	M - metastasis	
T1 - limited on the luminal side of capsule	N0 - no lymph nodes involvement	M0 - no distant spread	
T2 - limited capsule infiltration	N1 - one regional lymph node involved	M1 - distant spread	
T3 - cell aggregates infiltrating capsule	N2 - multiple nodes involved		
T4 - disease infiltrates beyond capsule			
Ann Arbour			
IA T1N0M0	IIA T4N0M0	III T4N1M0	IV T1-4N1-2M1
IB T2N0M0	IIB T1-3N1M0		
IC T3N0M0			

Table 1: Classification TNM Vs Ann Arbour from Clemens, et al. [25].

Case Report

We report a case of a 48-year-old Caucasian female with a history of bilateral cosmetic sub-muscular augmentation 11 years prior to this diagnosis. The implants used were Allergan textured, round, silicone implants (295cc; type ST110). The surgery was uneventful, and the operation details were available from the hospital notes. She presented with a 6 weeks history of left breast lump in August 2017. She has a medical history of right breast fibroadenoma that was biopsied in the past but not operated. With regards to her family history, her mother had breast cancer at age 65. She had 2 children and didn't breast feed. She used contraceptive pill (mini-pill) for more than 5 years and she was premenopausal at the time of presentation.

On clinical examination at presentation, there was a large lump in the upper-inner quadrant of the left breast, with no obvious sign of implant rupture on either side. The presence of focal asymmetrical lump was not typical of capsular contracture. Imaging was performed; mammogram showed no abnormality; ultrasound of the right breast confirmed the known right breast fibroadenoma whilst there were multiple masses in the left breast in the upper inner quadrant raising suspicion of ALCL; there was no associated seroma or fluid collection. An ultrasound guided biopsy was performed. MRI described an ill-defined lobulated mass measuring 46x35x40mm, in the upper inner quadrant anterior and

superior to the implant capsule, attached to the muscle. A small volume of fluid around the implant was reported. PET CT examination confirmed 6-7cm irregular mass adjacent to the supero-medial aspect of left breast implant with a cluster of small left axillary nodes and a small suspicious left internal mammary node. There was no evidence of disease elsewhere in the body. A core biopsy was performed from the left axillary lymph nodes.

Histology revealed focally highly pleomorphic infiltrate of neoplastic large cells, with prominent nucleoli; multiple mitoses were seen; background with small lymphocytes and numerous eosinophils; IHC confirmed strongly positive for CD30 and CD45, positive for CD2, CD4, CD5 and GranzymeB; CD3, CD7, CD5 and CD8 was largely confined to a background of small reactive T-cells. The neoplastic cells were ALK-1, AE1/3, CD56 and CK7 negative; MIB1 proliferation index was 80%.

Biopsy of the left axillary lymph nodes confirmed involvement of the lymph nodes. The final pathology was consistent with ALK-negative BIA ALCL with axillary lymph nodes involvement (stage IIB). The management was discussed in a multidisciplinary team including haematologists, oncologists, breast surgeons, hematology pathologist, breast pathologist and radiologist.

Pre-operative assessment of the disease showed potential unresectable disease, in discussion with thoracic

surgeon. Therefore, neoadjuvant chemotherapy was recommended with 6 courses of 2-weekly cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), followed by surgery and consolidation radiotherapy to the chest wall. PET CT performed post neoadjuvant chemotherapy showed complete radiological response in breast and lymph nodes, including internal mammary lymph node.

Surgery was performed consisting in bilateral removal of implants and capsulectomies under general anesthesia. Intraoperatively there was no residual mass/fluid collection found. The implant was removed "en masse" with the capsule. There was no obvious infiltration of the muscle. Contralateral surgery included right breast implant removal and capsulectomy. On macroscopic examination the right breast implant capsule was thinner, with no abnormality. No surgery was performed on the left axillary lymph nodes, given complete radiological response on PET-CT. The microscopic examination showed no evidence of malignancy on the left implant or capsule. The surgery was uneventful with no postoperative complications. Consolidation radiotherapy for the chest wall was recommended by the multidisciplinary team. The patient completed radiotherapy and she is planned to be reviewed every 3 to 6 months by the Haemato-oncologist for the next 5 years. The case was reported to the MHRA as per national guidance.

Discussion

The worldwide literature has reported few hundreds of cases so far and the reported incidence varies from 1/1000 and 1-3/1000000 [18,19]. The majority present with intracapsular disease and are treated with surgery alone. The pathology and immunohistochemistry findings confirm ALK negative and CD30 positive BIA ALCL; these cases are distinct from ALK negative systemic ALCL. The treatment usually consists of surgery [18]. The majority of BIA ALCL were diagnosed early and treated with surgery alone. Few advanced cases were reported in the literature and several deaths were registered. However, there is no recommendation for screening or prophylactic removal of breast implants for asymptomatic patients irrespective of family history or genetic predisposition for breast cancer [1].

The possible etiologic entities that have been proposed include chronic inflammation in response to a foreign body, genetic susceptibility as gene mutation, gene dysplasia and gene degeneration, microbiology

theory including unusual load of specific bacteria in the implant biofilm [1,19-23].

The cases reported so far demonstrated clinical presentation as seroma in 70% of cases, 30% as palpable mass and 10-17% had axillary lymphadenopathy corresponding to the side of the symptoms. Axillary metastasis was reported in 14,9% of cases. Usual laboratory investigations show unremarkable and non-specific features (isolated eosinophilia) [1]. Imaging investigations include ultrasound and MRI; the routine investigation is ultrasound, being useful for guidance in fluid aspiration for diagnosis. PET CT is the recommended investigation for staging and evaluation of systemic extent of the disease. Mammogram examination brings poor information on BIA ALCL [1,17]. The final diagnosis is based on immunohistochemistry analysis, BIA ALCL being ALK negative, CD30 positive and epithelial surface antigen positive. T cell antigens CD4 and CD43 are expressed in up to 85% of the cases; CD3, CD2 and CD45 are positive in around 30-35% of the cases and rarely there is expression of CD5, CD7, CD15, CD8 [1,5,12]. Evaluation, treatment and management of BIA ALCL should be decided by a multidisciplinary team, with experts familiar with this medical condition. NCCN guidelines are uncertain and were decided from series of case reports due to the rarity of this pathological entity and prospective studies are to follow [1,3].

Few cases of spontaneous remission for seroma have been cited in the literature with clinical surveillance [16,24]. Primary treatment includes surgical removal of the mass, the implant and capsulectomy and the aim is to acquire clear margins for oncology safety. If complete resection is achieved, no further adjuvant treatment is required [1,25]. Surgery should be performed guided by general oncology principles with orientation and marking of the specimen, marker clips in the remaining cavity. Guidelines suggest removing contralateral implant with capsule to prevent recurrent disease or lymphoma on the other breast [25,26].

Surgery to axilla needs not be performed routinely in the absence of evidence of nodal involvement. For cases with node enlargement, excision biopsy should be performed to confirm the pathology. More than a half of the patients with abnormal nodes showed metastatic disease in the reported literature [17,25].

The current NCCN guidelines recommend neoadjuvant chemotherapy with lymphoma regimes for mass presentation and locally advanced disease with lymph-

node involvement [1,3,25]. A retrospective study that included 87 patients with BIA ALCL compared surgery with chemo/radiotherapy approach and the disease-free interval in 3 years follow up was longer for patients who underwent surgery with complete resection. Adjuvant chemotherapy and radiotherapy is not usually recommended in cases of early disease and in cases where complete surgical removal is achieved [1,11].

Chemotherapy and radiotherapy as adjuvant therapy for incomplete resection had lower rates of survival and disease-free interval. The reported rate of recurrence in these cases is between 18 and 24% [1,24]. Oncology case reports suggest that Brentuximab regimens used for refractory disease can achieve complete remission and it is recommended as a first line treatment when chemotherapy needs to be avoided for toxicity reasons [18].

There is still a debate regarding axillary clearance in cases with neoadjuvant chemotherapy and possible benefit apart from removal of the implant and capsulectomy. The current indication for lymph-node removal is controversial and if complete radiological response has been achieved with CHOP regimens, then radiotherapy could be considered as adjuvant therapy to prevent recurrence, instead of axillary clearance. For women with nodal disease, a more aggressive approach is suggested, due to higher risk of recurrence [10,25].

A retrospective study reported 55 patients who underwent surgery for BIA ALCL [26]. 39 had adjuvant chemotherapy, 12 patients had watchful waiting and 4 patient had adjuvant radiotherapy. The outcomes were similar, and the survival rate and disease-free interval were higher for patients who had surgery with or without adjuvant chemotherapy. A comparison between patients presenting with a mass and those presenting with seroma showed that the survival rate and disease-free interval were higher for seroma cases. Patients presenting with breast mass who underwent complete resection of the tumor had similar rates of recurrence and survival rate or disease-free interval when compared to those with seroma presentation [2,18,25-27].

There are a few cases treated with radiotherapy alone and most of them were locally advanced [1,17,25]. Implant replacement remains controversial and it is not recommended, at least not with textured implants, but there were cited few cases of implant replacement with smooth textured implants. A close follow-up is recommended for those patients [1,17]. BIA ALCL

patients should be followed up clinically every 3-6 months for the first 5 years in a multidisciplinary team and annual ultrasound for the first two years. There are some reports suggesting CT thorax, abdomen and pelvis or PET CT every 6 months for the first 2 years [1,17,27].

Adjuvant chemotherapy or radiotherapy is recommended for disseminated disease, recurrent or incomplete surgical resection. Anthracycline chemotherapy regimens and immunotherapy with anti CD30 drug (Brentuximab) may be recommended as primary approach, however there is need for more data and multiple trials are ongoing. Regarding radiotherapy, the advantage of radiation therapy for primary cutaneous ALCL is well known, but the benefits are yet to be demonstrated for BIA ALCL. Radiotherapy alone has not been shown as efficient when complete resection is achievable [1,17,25,27].

Moreover, taking into consideration that worldwide there are 35 million patients with breast implants and only few hundred cases of BIA ALCL have been reported, there is no recommendation from any medical regulation society to remove the breast implants as preventative policy. Although the textured implants have been in the middle of the crisis related to the BIA ALCL and a few deaths were recorded related with this diagnosis, the risks and benefits of these medical devices are well known and acknowledged. Implant registry should be the next step in all countries using breast implants in order to record all patients and implants that are being used [28].

Most discussed risk factor for BIA ALCL still is the textured implants. Surgical technique, percentage of capsular contracture, strategies to improve sterility and operating time were demonstrated as no reliable factors to reduce the BIA ALCL risk. The constant of this discussion remains the textured implants. Few analyses were done recently and demonstrated that Biocell textured implants have the highest risk of BIA ALCL and FDA removed them as medical devices. Patients' groups and other medical professional groups are debating removal of textured breast implants as medical device, because no change in surgical technique or other modifiable factor from the implant pathway was demonstrated efficient to prevent BIA ALCL [29].

Research is being done currently to establish the clear pathogenesis of the disease. A possible theory includes an exacerbated immune response to the inflammatory microenvironment that releases cytokines and chemokines in the area and this pathway leads to seroma

formation. Mutation of JAK STAT 3 leads further to T cell proliferation. Although this mutation was found only in few cases, targeted therapy for JAK proteins warrant further research for the BIA ALCL and understanding of the pathogenesis [30]. Other pathogenesis pathway studied included lately the gram-negative microbiome, therefore use of antiseptic solution with broad spectrum tried to reduce this risk by irrigating the breast pocket. The pocket was prepared with both betadine and non-betadine solution and the betadine alone showed superior effect than others with higher bactericidal effect and improving inflammation [31].

In the available literature, complete surgical resection has the best outcome (4% risk of recurrence), when achieved. Poor prognosis includes bilateral disease, extracapsular extension of disease or mass presentation. [1,25,32].

Conclusion

In the case reported we wish to highlight the role of neoadjuvant chemotherapy in node positive and potentially unresectable disease, as primary surgery could have resulted in incomplete resection, potentially altering the prognosis.

It is also important to highlight the multidisciplinary approach with hematology and breast team, including surgeons, pathologists, radiologist and oncologist.

Currently patients in UK are being reported to MHRA as per indicated guidance (with similar registry in other countries) and this will help unify the data and provide insight from cases worldwide.

Although BIA ALCL is a very rare condition and the pathogenesis is not fully understood yet, early diagnosis and prompt surgical and oncological approach can be lifesaving for patients. The presentation with seroma around breast implants could potentially result in decision to revisional cosmetic surgery in the absence of adequate work-up. Therefore it is important to raise awareness and any swelling/ firm lump to be investigated prior to undertaking revisional surgery. Patients with breast implants, clinicians, and specialists in primary care should be trained to recognize and to act efficiently and responsibly if any suspicion [1,2,32].

Additional Information Section

Ethical approval and consent to participate: A local

ethics committee at the Oxford University Hospital ruled that no formal ethics approval was required in this particular case. The case was formally reported to MHRA as per national guidance.

Consent to publish: Patient has consented for anonymized data to be presented and published. Data Availability.

All medical data are provided in the manuscript.

Conflict of interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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The authors declare that the study was performed in accordance with the Declaration of Helsinki.

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