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Case Report

Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) - Case Report

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1. Abstract

Demand for aesthetic breast surgery is increasing worldwide, both for cosmetic reasons and postoperative breast reconstruction for breast cancer patients. Although the number of women with breast prostheses is steadily increasing, incidence rates for breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) are low, with an estimated incidence of 0.1-0.3 per 100,000 women with prostheses annually. Common clinical presentation of BIA-ALCL may include breast asymmetry, palpable mass, late seroma, local pain, and firmness. However, cytological examination of seroma fluid may reveal the condition, which should be followed by implant removal and total capsuletomy. In the majority of cases, capsulectomy is curative. Preoperative information about the risk of developing BIA-ALCL is recommended for patients with breast implants. Here, we report two BIA-ALCL cases, where one case was diagnosed after breast cosmetic surgery and the other patient had undergone breast reconstructive surgery with implants after breast cancer treatment.

2. Key words

Breast implant associated anaplastic large cell lymphoma BIA-ALCL; T-cell lymphoma; Breast aesthetic and reconstructive surgery; Capsulectomy

3. Introduction

An estimated 10 million women worldwide have breast implants and approximately 8,000 women undergo breast implantation in Sweden annually (80% aesthetic surgery and 20% reconstruction after breast carcinoma treatment) [1, 4, 5]. Over 1,000 BIA-ALCL cases have been reported to date, with 24 patient deaths [2, 3, 6]. The first cases of BIA-ALCL were reported in 1995 and 1997 [7, 8]. With an estimated risk of 1-3 women per million per year, BIA-ALCL incidence rates are on the rise as elective breast implantation is more commonly used [9]. Late accumulation of seroma fluid, pain, swelling and induration around an implant of more than 12 months of age may warrant a BIA-ALCL diagnosis. The average onset of seroma presentation is 8-9 years after implantation (range, 0.2 to 27 years) [10, 11]. The condition begins on the luminal surface of the fibrous capsule surrounding the implant (effusion limited disease, when anaplastic cells are confined to the fibrin layer overlying the capsule) and later may show varying degrees of infiltration of the capsule (Table 1) [12, 13]. This entity is multifactorial, primarily due to genetic factors (JAK/STAT3 activation and MYC/TP53 dysregulation, SOCS1 and DNMT3A mutations), Gram-negative biofilm around the implant, type of implant (mainly with textured surfaces), time and geographic differences (highest reported incidence is in Australia and New Zealand and an almost complete absence in Asian countries) [13-19]. Median overall survival rate is nowadays up to 93% and 89% 3- and 5-years after initial diagnosis, respectively [10].

4. Materials and Methods

Two patients aged 38 and 61 were diagnosed with Anaplastic Lymphoma Kinase (ALK)-negative BIA-ALCL at Sahlgrenska University Hospital, Department of Clinical Pathology (Gothenburg, Sweden). The first case developed after aesthetic surgery and the other was diagnosed after reconstructive breast implantation. Both patients had delayed, non-infective fluid collection around the breast implant. BIA-ALCL was diagnosed by cytological assessment

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of late chronic seroma fluid and later evaluated histopathologically in the fibrous scar tissue of the operation specimen adjacent to the implant. No bacteriological culture/microbiological examination either of seroma fluid or the specimen was performed. The study was approved by the Local Scientific Committee in Gothenburg (DNR: T1033 ad 287-15). The requirement for informed consent was waived by the ethical committee since patient materials were stripped from direct subject identifiers.

5. Case Report

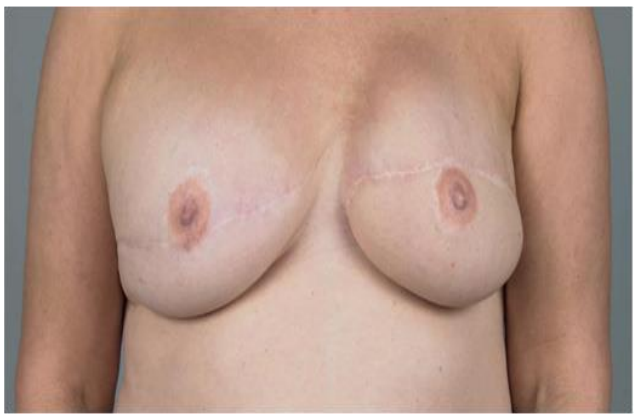
Patient No.1. In 1999, a 44 year old female patient underwent a left sided mastectomy for a luminal A-type of invasive ductal carcinoma NST (No Special Type), grade 2. A simultaneous contralateral prophylactic mastectomy was performed. The patient was initially reconstructed with permanent expander prosthesis bilaterally (Mentor Spectrum - Anatomical: McGhan Style 150 prosthesis) (Picture 1). A left side axillary metastasis of the breast carcinoma was identified in 2001, which was treated by irradiation. Due to complications on the irradiated left side, reconstruction with musculus latissimus dorsi flap was performed with implantation of a permanent prosthesis (McGahn MLP 260 cc) in 2003. The right permanent expander prosthesis was left in place. In neither of the operations were any antibiotics or antiseptic agents used. In

2016, the patient (61 years of age) developed an ALK-negative BIA-ALCL in the thickened fibrotic capsule around the right side implant, which was verified with cytological assessment of the seroma fluid. Both implants were removed together with the fibrotic capsule (Figure 1). The anaplastic lymphoid cells infiltrated the whole thickness of the capsule with tumor necrosis as in stage T3 (Table 1). No lymphadenopathy was found. No further adjuvant therapy was given. She was free of the disease four years later (Picture 2).

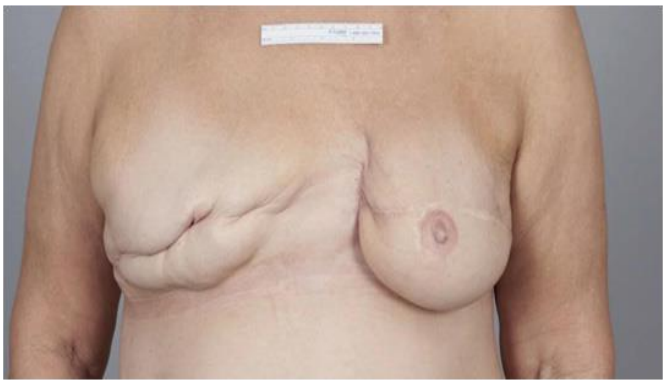
Patient No.2. The patient underwent bilateral breast augmentation in 2006, and the prostheses were later replaced with bigger ones in 2008. In 2015, the patient experienced swelling of the right breast, which led to replacement of the right side implant again by the private plastic surgeon. In 2016 at the age of 38, an ALK-negative BIA-ALCL was diagnosed in thepatient´s right breast in a late seroma. Bilateral removal of the implants with total capsulectomy was performed (Figure 2). No data about the type of prostheses or the performed surgical procedure was available from the private clinic. Lymphoma cells superficially infiltrated the luminalside of the capsule, as in stage T2 (Table 1). Postoperatively, the patient received radio- and chemotherapy. The patient developed a recurrence of BIA-ALCL medially on the chest wall which indicated a more radical capsulectomy performed by a breast surgeon 7 months later in 2017 and the patient was again treated with radio- and chemotherapy (CHOP: cyclophosphamide, doxorubicin, vincristine, prednisolone). No lymphadenopathy was identified. The patient is disease free after three years of follow-up.

Table 1: Recommended staging system, adapted from Clemens et al. (2).

TNM Stage	Description
Tumor extent	
T1	Lymphoma cells confined to the effusion or a layer on luminal side of the capsule
T2	Superficial infiltration of lymphoma cells on luminal aspect of the capsule
T3	Sheets or clusters of lymphoma cells infiltrate into the thickness of the capsule
T4	Lymphoma cells infiltrate beyond the capsule into the adjacent soft tissue or breast parenchyma
Lymph node	
N0	No lymph node involvement
N1	One regional lymph node (+)
N2	Multiple regional lymph nodes (+)
Metastasis	
M0	No distant spread
M1	Spread to other organs/distant sites



Picture 1: Patient No.1. Bilateral breast reconstruction was performed in 2003 before the BIA- ALCL diagnosis. The right breast mound is the result of a prophylactic skin sparing mastectomy with permanent expander. The left side was reconstructed with a delayed musculus latissimus dorsi flap and permanent implant. The patient was given bilateral nipple tattoos.



Picture 2: Patient No.1. The appearance of the chest wall after the BIA-ALCL diagnosis in 2019. The patient underwent bilateral removal of the implants as well as complete capsulectomies. The right side shows redundant mastectomy skin following breast implant removal with indrawn skin flaps. The left side shows a smaller deformed breast mound after removal of the implant. The remaining reconstructed left breast mound and volume is due to the musculus latissimus dorsi flap.

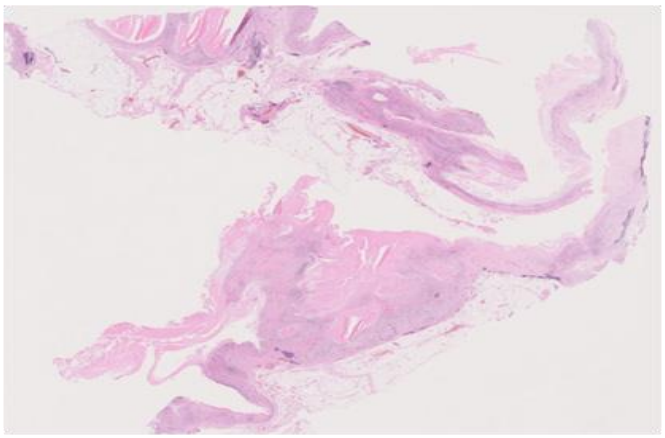


Figure 1: Patient No.1. Clusters of sheets of lymphoma cells: infiltrate into the whole thickness of the capsule with tumor necrosis, stage T3 (5x magnification).

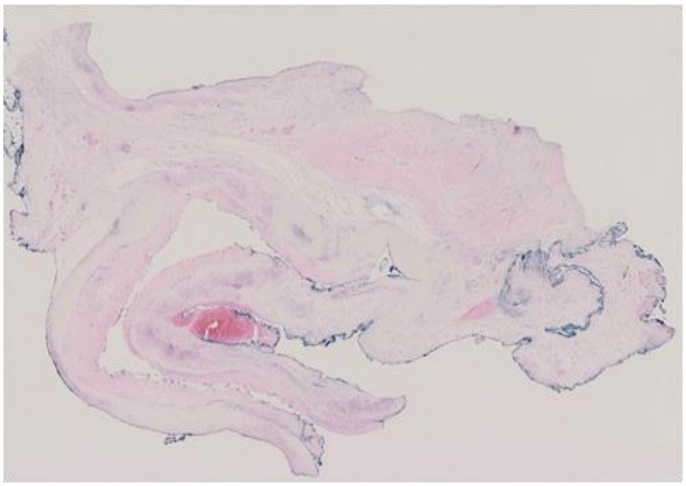


Figure 2: Patient No.2. Lymphoma cells superficially infiltrate the luminal side of the capsule, stage T2 (5x magnification).

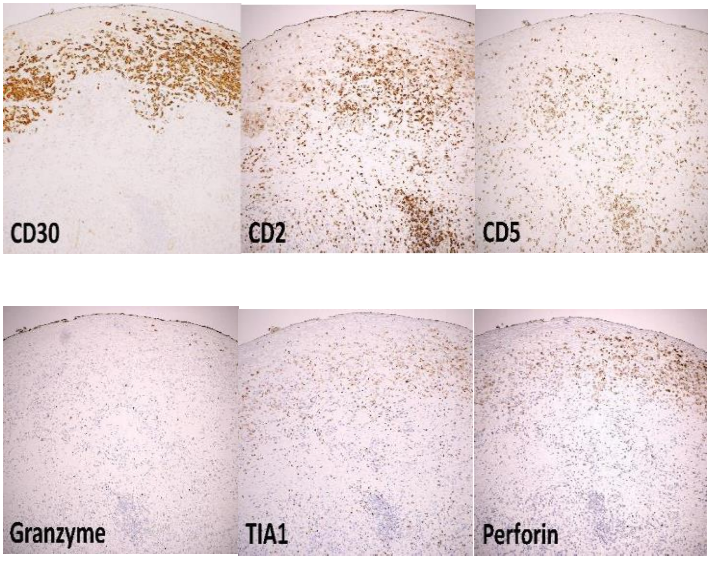


Figure 3: Patient No.2. Immunohistochemical analysis of the fibrous capsule. Anaplastic cells expressed CD30, CD2, CD5 and cytotoxic-associated antigens such as Granzyme, TIA1 and Perforin (100x magnification).

6. Results

Microscopic analysis revealed monoclonal T-cell proliferation with appearance of pleomorphic epithelioid cells with blast-like morphology. Consequently, severe atypia was found in both cases, both in the seroma fluids and in the fibrotic capsules around the implants. The immunocyto-/histochemical analysis showed positivity for CD45, CD30, CD8, and cytotoxic- associated antigens such as Granzyme, TIA-1 and Perforin in the large anaplastic cells obtained from seroma fluids and in the fibrous capsule of the surgical specimens. Negative results were found for ALK-1, CD3 and CD20. Complete surgical excision, including bilateral total capsulectomy with breast implant removal, had been performed for both patients and they have 3- and 4-year disease-free survival, respectively.

7. Discussion

Approximately 55,000 breast prostheses are implanted for reconstructive and cosmetic purposes in the United States annually [10, 20]. BIA-ALCL is a rare, but highly treatable type of T-cell lymphoma that can develop as late periprosthetic effusion only (measuring from 20 cc to 1,000 cc) or in combination with a palpable mass, or a breast mass alone. It can even present without a seroma or mass, but with detectable lymph node involvement or it can develop in the subcutaneous breast tissue. A case of BIA-ALCL has been reported by a transgender female [21] and gluteal implant associated-ALCL has been also described [22].

BIA-ALCL is a T-cell type of non-Hodgkin lymphoma, which differs from other breast lymphomas, as these are most frequently of B-cell type [9]. It is characterized by the presence of a monoclonal population of uniformly CD30-positive, large anaplastic cells, ALK-negativity and variable expression of T-cell markers and epithelial membrane antigen (EMA). One case with breast implant–associated plasmablastic lymphoma has been reported [23]. In 2016, the World Health Organization (WHO) recognized BIA-ALCL as a provisionally distinct entity, which differs from other ALK-negative ALCLs [11]. Moreover, FDA acknowledged the link between breast implants and ALCL in 2017 [24].

Clemens *et al.* recommended a staging system (stages 1-4) for BIA-ALCL's, whereby stage 1 comprises effusion only and/or infiltration of the luminal surface of the fibrous capsule around the implant, and stage 4 when lymphoma cells infiltrate beyond the capsule into the adjacent soft tissue or breast parenchyma [2]. Similarly, Kadin *et al.* postulated that BIA-ALCL might be part of the spectrum of a CD30+ lymphoproliferative disease ranging from an *in situ* tumor stage (confined within the seroma) with low malignant potential, to an invasive malignant lymphoma (with or with-

out periprosthetic effusion) [13]. As two Australian cases of spontaneous regression and resolution have been reported, the question arose whether cases of "seroma-only disease" without capsular involvement (stage T1) might represent a self-limiting lympho-proliferative disorder and not malignancy [25].

The importance of different implant types (textured or smooth devices) has been debated as a causative factor of the disease. Our first patient had a permanent expander on the affected side (Mentor Spectrum-Anatomical:McGhan Style 150 prosthesis), but we had no information about the implant type. Patients with textured breast implants have a higher risk of developing BIA- ALCL, but also malrotation, double capsules and increased bacterial growth [6, 20]. Some plastic surgeons in the US defended the use of textured breast implants which caused fewer capsular contractures, especially when the Adams's 14-point plan was used to improve sterility during implantation [26]. However, Swanson et al. concluded that textured implants as a device was the problem, rather than the surgical technique. In spite of this, FDA lifted the ban on textured breast implants, possibly to avoid a groundswell of patients requesting removal or replacement of their implants [6].

Although the etiology of BIA-ALCL is unknown, an initiating inflammatory stimulus, including infection may trigger the development of BIA-ALCL, which starts at the luminal aspect of the capsule around breast implants [10] [27, 28]. Lymphomagenesis might be caused by chronic inflammation induced by capsule surface and contents (silicon leechables/bleeds and particles, chemically active agents like metals, vinyl derivatives, xylol) [9, 24]. Bacterial biofilm may induce an intense T-cell response, predominantly with type 17 helper T-cell (Th17) /Th1 signature. Even a Th2 allergic inflammatory response is suggested by the presence of IL-13, eosinophils and IgE-coated mast cells [18, 11]. Interleukin-6 receptor signaling was attributed as a major driver of BIA-ALCL [29]. Microbiome analysis of breast implants and periprosthetic tissue in BIA-ALCL revealed mainly Gram-negative bacteria (e.g. Ralstonia pickettii), but even Gram-positive Staphylococcus saprophyticus (including S. epidermidis) and Cutibacterium acnes (formally Propionibacterium acnes) have been identified, known as members of the normal skin microflora [19]. Walker et al. concluded that no consistent differences were seen between bacteria identified in BIA-ALCL specimens compared with contralateral control breasts [18, 20]. No data from microbiological analyses of the seroma fluid are available. Identification of ribosomal protein S10 in a BIA-ALCL specimen may suggest viral etiology [11]. case of synchronous BIA-ALCL and invasive breast carcinoma has been described and next generation sequencing revealed diverse genetic alterations, including an activating STAT3 mutation in the lymphoma and a PIK3CA in-frame deletion in the breast carcinoma [30]. This case emphasizes the importance of a thorough clinical examination for concomitant malignancies of the breast when BIA-ALCL is diagnosed. Early diagnosis of premalignant conditions in the evolution of benign late seromas to BIA-ALCL might allow earlier identification and intervention, preventing the development of an invasive disease [13]. In addition to CD30, interleukins could also be used for diagnostic purposes, as IL-9, IL-10 and IL-13 are able to distinguish malignant and benign seromas [16].

When the disease is limited to the fibrous scar tissue, removal of the implant followed by en- bloc capsulectomy is curative. The BIA-ALCLs described here were stage T3 and T2, respectively. In the first case, bilateral removal of the implants with complete capsulectomy proved to be curative, but in the second case recurrent disease had developed in spite of bilateral implant removal with capsulectomy, radio- and chemotherapy. Removal of the contralateral implant is advisable since incidental contralateral BIA-ALCL has been reported. Implantation of a new breast prosthesis is not recommended after BIA-ALCL has been diagnosed, in those cases autologous options are preferable [31, 32]. When complete capsulectomy with no residual disease is achieved, clinical follow-up should be done every 3-6 months for two years, and thereafter as clinically indicated. In our cases, the patients currently have 3-4 year disease free survival. Incomplete capsulectomy or chest invasion warrants radiotherapy [9, 14].

Brinton et al. analyzed the association of breast implants with other malignancies besides BIA- ALCL. Slightly higher rates of cervical, vulvar, gastric, cerebral tumors and leukemias were found in more than 13,000 women with breast implants, but the differences have been attributed to different lifestyles [33, 24].

8. Conclusion

Women should be aware of BIA-ALCL preoperatively. Therefore, clinicians should inform patients about the risks of breast implants used in augmentation mammoplasty [34].

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