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Anaplastic Large T-Cell Lymphoma Associated with Breast Implants – Rare Disease

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Globally, breast cancer is the most frequently diagnosed cancer and is the leading cause of cancer death in women. Primary lymphoma of the breast is extremely rare, accounting for 0.04 to 0.5% of all breast malignancies and approximately 1 to 2% of all extranodal lymphomas. Most non-Hodgkin's lymphomas involving the breast are of B-cell origin. Less than 10% of breast non-Hodgkin's lymphomas are of T-cell lineage. Only 6% of all T-cell lineage lymphomas are diagnosed as anaplastic large cell lymphomas (ALCL). Hence, naturally occurring (not implant-related) ALCL of the breast accounts for about 6:1,000,000 cases of breast malignancies [1].

Breast implants are widely used for aesthetic breast augmentation and for breast reconstruction. Despite the widespread use of breast implants, the prevalence of implant complications is low. General complications include capsular contracture, rupture, leakage, infection, migration of the implant and late seroma. Within this overall context, a possible association between breast implants and the development of a distinct form of ALCL has recently been identified [2]. To the best of our knowledge, we present the first reported case in Israel of breast implant-related ALCL (BIR ALCL).

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PATIENT DESCRIPTION

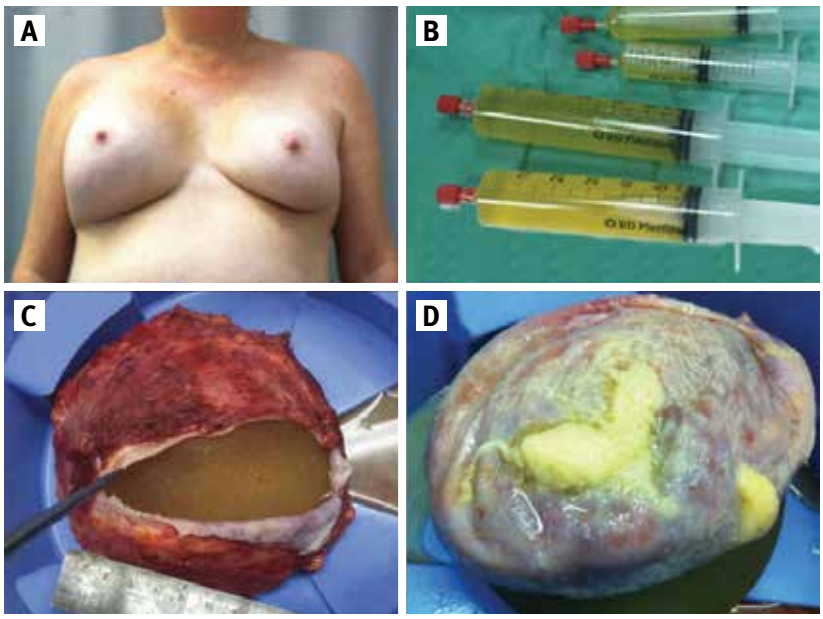
A 51 year old woman with breast implants was admitted to our department due to sudden unilateral right breast enlargement and discomfort [Figure 1A]. Breast augmentation had been performed 11 years earlier, with sub-glandular placement of allergan-textured silicone breast implants. The postoperative period and routine breast imaging were normal.

The woman denied any history of breast trauma, prodromal illness, pain, local sign of infection, night sweats, weight loss, poor appetite or fever.

On physical examination breast asymmetry was obvious. The right breast was swollen, firm and sensitive. The left breast was normal. No signs of local infection were observed. Initial blood analysis, including blood count, chemistry, C-reactive protein, lactate dehydrogenase (LDH) and blood culture, were all normal.

Upon admission to our facility, we performed a breast ultrasound. In the right breast a large amount of periprosthetic proteinaceous fluid was found with capsular thickening. The implant was intact and no mass was seen. The regional lymph nodes were not enlarged. Examination of the left

Figure 1. [A] Unilateral right breast enlargement 11 years after breast augmentation, **[B]** yellowish periprosthetic serotic fluid drained from the right breast, **[C]** implant and periprosthetic capsule removed as a whole after total capsulectomy, **[D]** fibrinoid material containing malignant cells on the inner surface of the periprosthetic capsule



breast demonstrated an intact implant and no mass was seen. Several lymph nodes with thick cortex were noted.

During hospitalization several percutaneous fluid aspirations under ultrasound guidance were performed. We drained a total of 410 ml of yellowish serotic fluid (Figure 1B). The fluid was sent to the cytology laboratory for blood count, chemistry and blood culture analysis. Chemical analysis demonstrated exudative fluid with a high level of LDH, blood cell counts were normal and fluid cultures were all negative.

Cytology analysis of the aspirated fluid revealed atypical lymphoid cells suspicious for high-grade lymphoma. Cellblock staining revealed that CD3, CD30 and CD45 were positive, while CD4, CD8, CD7, CD20, and anaplastic lymphoma kinase (ALK) 1 were negative. T-cell rearrangement was positive and demonstrated monoclonality. Karyotype testing using Giemsa-banding (G-banding) staining revealed multiple complex chromosomal changes.

A positron emission tomography – computed tomography (PET/CT) exam showed a localized disease with low standardized uptake value (SUV) in the fluid surrounding the right breast implant.

The patient underwent bilateral total capsulectomy to remove the capsule and the implants as a whole (Figure 1C). The capsule was sectioned and sent for pathological evaluation. On the inner surface of the periprosthetic capsule, a fibrinoid material was observed (Figure 1D). The pathology results confirmed the diagnosis of anaplastic T-cell lymphoma, revealed as CD30-positive ALK 1-negative and confined to the fibrinoid material next to the prosthesis. The fibrous capsule and the soft tissue were tumor free.

At the time of this publication, we completed 2 years of postoperative follow-up with no clinical, laboratory or imaging signs of residual or recurrent lymphoma.

COMMENT

Breast implants have been in common use for aesthetic and reconstructive procedures for over 50 years. Although there has been a concern regarding a possible elevated risk of breast carcinoma, no evidence of a causal association between silicone and cancer was found.

Recently, a possible association between breast implants and the development of a distinct form of lymphoma – BIR ALCL – has been identified. ALCL of the breast is a very rare finding that has mainly been described in the literature as case reports. The first case of BIR ALCL was described in 1997. Since then, according to the U.S. Food and Drug Administration over 350 known cases of ALCL in women with breast implants have been reported worldwide [2].

Clinically, most cases present with sudden unilateral breast swelling. The swollen breast can be asymptomatic or it may be painful and associated with a rash and pruritus. Patients rarely report fever, loss of appetite, weight loss and night sweats, which can suggest the presence of disseminate disease.

On physical examination, the breast may be firm and sensitive to palpation. In the minority of cases a solid breast mass and lymphadenopathy may be found. Capsular contraction, erythematous skin eruption, and lymphomatoid papulosis of the breast are rarely observed. The mean time interval from initial breast implant surgery to diagnosis was approximately 9 years, with a range of 1 to 23 years [3].

The clinical behavior of BIR ALCL can be divided into two major subtypes [4]:

- Effusion-associated ALCL (EA ALCL), characterized by the presence of malignant cells found in the periprosthetic fluid, lining the capsule border or embedded within the fibrinoid material within the perifrothetic capsule
- Solid tumor limited to the breast and diffuse infiltration of the capsule and adjacent tissue (less frequent)

According to the available data, patients who present with EA ALCL have an indolent disease course and the prognosis is excellent, with more than 90% of cases achieving complete remission if the breast implant and fibrous capsule are removed. In contrast, patients who present with a distinct mass may have a more aggressive disease and an increased risk for local recurrence. Complete remission was achieved in 72% of these cases after chemotherapy [5].

Since very limited clinical data are available, it is hard to determine the pathogenesis of implant-related ALCL. A review of the literature reviled no distinct pattern linking BIR ALCL to the type of surgery (aesthetic vs. reconstructive) or the type of the implant (silicone-filled or saline-filled silicone-coated devices). Nevertheless, nearly all cases of BIR ALCL were found in correlation with implants having a textured outer shell rather than a smooth outer shell [6]. A number of hypotheses have been proposed. It has been speculated that micro-silicone particles might detach from the textured shell and incite a chronic inflammatory response to instigate neoplastic transformation [6]. In addition, biofilm infection was also proposed as a possible cause of chronic inflammation leading to genetic transformation [6].

Currently, there is no evidence-based consensus for management of BIR ALCL. In cases of breast swelling, periprosthetic fluid should be sent for cytological examination. In cases of ALCL suspicion, consultation with an experienced hematopathologist is recommended. The fluid should be sent for further genetic, molecular biology and flow cytometry analysis to assess the lymphoma characteristic. PET/CT should be conducted to exclude primary and secondary malignancy and the presence of systemic disease. In cases of effusion associated ALCL, total capsulectomy and implant removal as a whole is recommended, and usually no additional treatment is needed [5]. In cases of clinical or radiological evidence of a solid mass or lymphadenopathy, a multi-disciplinary management approach is recommended, including surgical, hematological, radiological and oncological consultation.

In cases of extracapsular breast lymphoma, multi-agent chemotherapy with

or without radiation is suggested. Some reports of bone marrow transplantation in cases of disseminated disease have been described. Due to lack of clinical trials, the systemic therapy approach still needs to be defined [5].

CONCLUSIONS

In conclusion, we present what we believe to be the first case of BIR ALCL in Israel. In cases of late unilateral breast swelling after implant surgery, the entity of implant-associated ALCL should be considered. Every specimen should be sent for cytological evaluation with emphasis on the probability of ALCL, as early diagnosis and surgical approaches may result in a positive outcome for patients diagnosed with the disease. Due to a lack of clinical data, it is important to continue investigating and collecting information to understand the nature and possible factors contributing to ALCL in women with breast implants.

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References

1. Gidengil CA, Predmore Z, Mattke S, et al. Breast implant-associated anaplastic large cell lymphoma: a systematic review. *Plast Reconstr Surg* 2015; 135: 713-20.
2. U.S. Food and Drug Administration. Anaplastic large cell lymphoma (ALCL) in women with breast implants: preliminary FDA findings and analyses. Center for Devices and Radiological Health, Silver Spring, MD 2011. Available at: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239995.htm
3. Jewell M, Spear SL, Largent J, Oefelein MG, Adams Jr WP. Anaplastic large T-cell lymphoma and breast implants: a review of the literature. *Plast Reconstr Surg* 2011; 128 (3): 651-61.
4. Laurent C, Delas A, Gaulard P, et al. Breast implant-associated anaplastic large cell lymphoma: two distinct clinicopathological variants with different outcomes. *Ann Oncol* 2016; 27 (2): 306-14.
5. Miranda RN, Aladily TN, Prince HM, et al. Breast implant-associated anaplastic large-cell lymphoma: long-term follow-up of 60 patients. *J Clin Oncol* 2014; 32: 114-20.
6. Brody GS, Deapen D, Taylor CR, et al. Anaplastic large cell lymphoma occurring in women with breast implants: analysis of 173 cases. *Plast Reconstr Surg* 2015; 135: 695-705.

Capsule

Regulating the regulators

Inhibitory receptors on T cells, including *lymphocyte-activation gene* 3 (encoded by LAG3) limit immune-mediated damage to the host. LAG3 is expressed by exhausted conventional T cells in the tumor microenvironment. The role of LAG3 in regulatory T cells (T_{reg}) has remained unclear. Zhang et al. studied a mouse model of autoimmune diabetes. T_{reg}-specific deletion of LAG3 led to enhanced T_{reg} proliferation and reduced the incidence of type 1 diabetes. The findings highlight the cell-type dependence and context specificity of LAG3 and call for a more holistic assessment of the functions of inhibitory receptors that are emerging as targets for tumor immunotherapies.

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Capsule

Conversion of adult endothelium to immunocompetent hematopoietic stem cells

Developmental pathways that orchestrate the fleeting transition of endothelial cells into hematopoietic stem cells remain undefined. Lis et al. demonstrated a tractable approach for fully reprogramming adult mouse endothelial cells to hematopoietic stem cells (rEC-HSCs) through transient expression of the transcription-factor-encoding genes *Fosb*, *Gfi1*, *Runx1*, and *Spi1* (collectively denoted hereafter as FGRS) and vascular-niche-derived angiocrine factors. The induction phase (days 0–8) of conversion is initiated by expression of FGRS in mature endothelial cells, which results in endogenous *Runx*1 expression. During the specification phase (days 8–20), RUNX1+ FGRS-transduced endothelial cells commit to a hematopoietic fate, yielding rEC-HSCs that no longer require FGRS expression. The vascular niche drives a robust self-renewal and expansion phase of rEC-HSCs (days 20–28). rEC-HSCs have a transcriptome and long-term self-renewal capacity similar to those of adult hematopoietic stem cells, and can be used for clonal engraftment and serial primary and secondary multi-lineage reconstitution, including antigen-dependent adaptive immune function. Inhibition of TGFβ and CXCR7 or activation of BMP and CXCR4 signal enhanced generation of rEC-HSCs. Pluripotency-independent conversion of endothelial cells into autologous authentic engraftable hematopoietic stem cells could aid treatment of hematological disorders.

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Eitan Israeli

"Our prime purpose in this life is to help others. And if you can't help them, at least don't hurt them"

Dalai Lama (born 1935), leading monk of the Gelug school, the newest school of Tibetan Buddhism