How Common Is Breast Implant-Associated Anaplastic Large Cell Lymphoma? First Four Cases in Israel

Yeela Ben Naftali MD, Yoav Barnea MD, Mark W. Clemens MD and Eran Bar-Meir MD

1Department of Plastic and Reconstructive Surgery, Rambam Health Care Campus, affiliated with Technion-Israel Institute of Technology, Haifa, Israel
2Department of Plastic and Reconstructive Surgery, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
3Department of Plastic Surgery, University of Texas MD Anderson Cancer Center, Houston, Texas, USA
4Department of Plastic Surgery, Padh Medical Center, Poitou, Israel
5Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
6Faculty of Medicine, Bar-Ilan University of the Galilee, Safed, Israel

ABSTRACT: Background: Breast implant-associated anaplastic large cell lymphoma (ALCL) is a rare type of non-Hodgkin's lymphoma that is found around breast implants. ALCL was discovered only two decades ago. In Israel we have had four diagnosed cases (as of 2018). Up to recently, the estimated incidence was 1,300,000 women with breast implants, while recent reports range from 1,3817 to 1,381,000.

Objectives: To determine the occurrence of breast implant-ALCL in Israel.

Methods: We conducted a retrospective analysis of the four patients diagnosed with ALCL in Israel. Cytology was confirmed and the clinical data was collected. Based on the estimated number of women with breast implants in Israel, a calculation of the true incidence was completed.

Results: The incidence in Israel is significantly higher than the older incidence reports indicate. We estimated that the lifetime prevalence of the disease is 4,600,000 women with a textured breast implant, or 1,15,000 women with a textured breast implant in Israel.

Conclusions: ALCL is not common. We support the claim that the prevalence is significantly higher than what was initially described. This finding has clinical and medicolegal implications that should be addressed accordingly.

KEY WORDS: anaplastic large cell lymphoma (ALCL), breast cancer, breast implant-associated anaplastic large cell lymphoma (BIA-ALCL), non-Hodgkin's lymphoma

For Editorials see page 516 and page 517

First described in 1962, silicone prosthesis implantation has become a common practice in aesthetic or reconstructive breast surgery [1]. Thirty-five years later, in 1997, Keech and Creech [2] described the first case of anaplastic large cell lymphoma (ALCL). The patient was implanted with a McGhan (formerly Allergan, USA) textured saline prosthesis. Following this diagnosis, the patient underwent implant replacement and capsulectomy, chemotherapy, and radiotherapy. Does this diagnosis signal the end of an era or is it just a rare phenomenon?

Breast implant-associated ALCL is a rare type of non-Hodgkin’s lymphoma that is found around breast implants. Nearly all breast implant-associated ALCL patients have early-stage disease. Only six bilateral cases were published globally, and until recently the incidence was estimated between 0.1 and 0.3 per 100,000 women with prostheses annually [3-5]. While the newest report estimates are 1,3817 to 1,381,000 [6,7], the exact number of cases remains difficult to determine due to limitations in world-wide reporting and sales data [3-6].

ALCL occurs around textured implants [8,9] on average 9 years after implantation. The mean age at the time of diagnosis is 53.2 years [3]. The first manifestation is typically late seroma (67.33%), followed by mass (22.1%) and lymph node involvement (13.8%) [10].

Pre-operative fine needle aspiration (FNA) is preferred if fluid is found around the breast implant, and a biopsy is conducted in the case of a mass being found. Cytology is essential for diagnosis, specifically CD30 cell surface protein is highly expressed in addition to ALK-1 negativity [5]. The National Comprehensive Cancer Network (NCCN) guidelines advise complete surgical excision of the surrounding fibrous capsule as the treatment of choice [11,12]. Any associated mass must be excised and suspicious nodes biopsied. Removal of the contralateral implant needs to be considered. Disseminated disease or cases of incomplete excision should be treated by adjuvant radiotherapy and systemic therapy [5,10,12-14].

Only a few patients developed aggressive disease. In most of the cases the disease was confined to the capsule [10,12,15]. The management involved a multidisciplinary team, medical history, physical exam, blood test results, and positron-emission tomography/computed tomography (PET/CT) [5]. There are still inconsistencies among the reports, diagnosis, and treatment of ALCL [16]. Follow-up, medical history, and physical

Conflict of interest statement: Dr. Barnea is a speaker for Johnson Medical
exam are performed every few months for a 2-year period. CT scans are performed at physician's discretion, based on clinical indication [11]. The pathogenesis is still unclear, although a pathogenic mechanism of chronic T-cell stimulation with local antigenic drive may be involved in the development of the disease [9].

The recent estimation is that the lifetime prevalence of the disease is between 1:3817 and 1:30,000 [3,6,7]. The objectives of the article were to determine the occurrence of breast implant-associated ALCI in Israel. A retrospective analysis of four patients with ALCI was conducted. Israel is a small country with an organized health system; therefore, our results may be a good example of the global prevalence.

PATIENTS AND METHODS

STUDY DESIGN

To identify all cases of ALCI in Israel, we performed a review of the literature, made direct communication with every plastic surgery department in the country, and communicated with all plastic surgeons via the plastic surgery association network. Four cases of ALCI were identified in 2018. We requested clinical information, pathology reports, treatment protocol, and follow-up data from the corresponding surgeons of all four cases.

PATIENT CHARACTERISTICS

The four patients who were diagnosed with ALCI in Israel were 37–51 years of age. Three of them were healthy, whereas one presented with diabetes, hypertension, hyperlipidemia, and smoking addiction. Three had Allergan implants. One patient underwent two implant surgeries: the first with an Allergan implant, the second with Mentor. The implants were placed subglandular in three cases and subpectoral in one case.

STATISTICAL ANALYSIS

We determined the Israel incidence of breast implant-associated ALCI overall from 1948 to 2017. Textured implants were first introduced in Israel in 1980. The incidence was determined using the number of newly diagnosed cases and the number of breast implants in the Israel population. We estimated the number of breast implants in the population, which was based on data from the implants company compared to the overall breast implant-associated ALCI incidence rates that were previously reported in the United States.

RESULTS

Occurring 7 to 12 years after implantation, late seroma was the initial presentation for the four ALCI diagnoses, with no history of trauma, pain, inflammation, or physical findings. The Initial workup included ultrasound and cytology evaluation for the fluid collection. In all four cases, CD30 was positive, Alk-1 was negative, and histological examination presented abnormal morphology with large anaplastic cells [Figure 1]. Surgical treatment included bilateral breast implant removal and capsulectomy.

In all of the cases, PET/CT examination was performed with unremarkable findings. No further adjuvant chemotherapy or radiotherapy was needed. Patients continued oncology follow-up. The capsule gross examination and histological reports were normal [Table 1].

INCIDENCE OF BREAST IMPLANT-ASSOCIATED ALCI GLOBAL

In January 2011 the U.S. Food and Drug Administration (FDA) safety communication published the report, Women with breast implants may have a very small but increased risk of developing this disease in the scar capsule adjacent to the implant, which was based on 34 patients. In January 2016, the FDA published an update based on 258 cases reported (volunteer basis), which estimated 100–250 cases in the United States. The last update was published 21 March 2018 [6]. The FDA has received reports on a total of 414 cases worldwide, including nine deaths. The current FDA policy confirms that patients with breast implants do not need to change their routine medical care and follow-up procedures. The FDA suggests that due to the information that was published in the latest update, women with breast implants have a very low, but increased risk of developing ALCI, compared to women who do not have breast implants [6].

LIFETIME PREVALENCE OF BREAST IMPLANT-ASSOCIATED ALCI IN ISRAEL

Based on annual sales data, we estimated that there were approximately 60,000 women with textured breast implants in Israel by 2017 (aesthetic or reconstructive). In this article, we describe the first four cases of breast implant-associated ALCI.

Figure 1. Highly atypical lymphoid cells with enlarged irregular nuclei, irregular chromatin abundant cytoplasm, and numerous mitosis (arrowed) some cells show anaplastic features (double arrow)
Table 1. Clinical data of the four first cases of breast implant anaplastic large cell lymphoma in Israel

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>46</td>
<td>61</td>
<td>48</td>
<td>37</td>
</tr>
<tr>
<td>Background</td>
<td>Healthy</td>
<td>smoker with diabetes, hypertension, and hyperlipidemia</td>
<td>Healthy</td>
<td>Healthy</td>
</tr>
<tr>
<td>Implant company</td>
<td>Allergan 340 gr silicone, textured</td>
<td>Allergan 460 gr silicone, textured</td>
<td>First surgery: Allergan, textured. Second surgery: Mentor, textured</td>
<td>Inspira®, textured</td>
</tr>
<tr>
<td>Implant pocket</td>
<td>Subglandular</td>
<td>Subglandular</td>
<td>Subglandular</td>
<td>Subpectoral</td>
</tr>
<tr>
<td>Years with implant</td>
<td>12</td>
<td>11</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Late seroma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Trauma, pain, other physical findings</td>
<td>no trauma, no pain, no inflammation, no physical findings</td>
<td>no trauma, no pain, no inflammation, no physical findings</td>
<td>no trauma, no pain, no inflammation, no physical findings</td>
<td>no trauma, no pain, no inflammation, no physical findings</td>
</tr>
<tr>
<td>Pre-operation ultrasound</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PET/CT exam</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD30 positive, ALK-1 negative</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Surgery</td>
<td>Bilateral implant removal and capsulectomy</td>
<td>Bilateral implant removal and capsulectomy</td>
<td>Bilateral implant removal and capsulectomy</td>
<td>Bilateral implant removal and capsulectomy</td>
</tr>
<tr>
<td>Capsule pathological exam</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>Oncology follow up</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Additional treatment</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Genetic background and ethnicity</td>
<td>Caucasian, Jewish</td>
<td>Caucasian, Jewish</td>
<td>Caucasian, Jewish</td>
<td>Caucasian, Jewish</td>
</tr>
</tbody>
</table>

*Inspira implants are made by Allergan*


<table>
<thead>
<tr>
<th>Country</th>
<th>Incidence of anaplastic large cell lymphoma</th>
<th>Implant type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Israel</td>
<td>1:15,000</td>
<td>Biocell®</td>
</tr>
<tr>
<td>United States</td>
<td>1:30,000</td>
<td>Biocell®, Silite®</td>
</tr>
<tr>
<td>Australia</td>
<td>1:3245</td>
<td>Biocell®, Polyurethane</td>
</tr>
<tr>
<td></td>
<td>1:2832</td>
<td>Silite®</td>
</tr>
<tr>
<td></td>
<td>1:96,029</td>
<td>Textured implants</td>
</tr>
<tr>
<td>Netherlands</td>
<td>1:8900</td>
<td>Textured implants</td>
</tr>
<tr>
<td>Canada</td>
<td>1:22,000</td>
<td>Textured implants</td>
</tr>
</tbody>
</table>

Biocell implants are produced by Allergan, Inamed, McGhan, Cult; Silite by Mentor; and Polyurethane by Sillmed

in Israel. The lifetime prevalence of the disease was 4:60,000 women with a textured breast implant, or 1:15,000 women with a textured breast implant.

**DISCUSSION**

Breast implant associated ALCL is a rare type of non-Hodgkin’s lymphoma, which tests positive for CD30 and negative for ALK-1 in the fluid surrounding the implant. In most cases, there is no evidence of a metastatic disease; hence, surgical treatment that includes breast implant removal and total capsulectomy, is usually sufficient [10-14,17]. Some of the cases may regress spontaneously without treatment [18]. While disease etiology is unknown, a number of hypotheses regarding its cause have been considered, including genetic predisposition, silicon particles, and biofilm [6,19]. Recently Allergan plc (Dublin, Ireland) announced that they were suspending sales and withdrawing supply of all textured breast implants in the European markets [20].

The four cases from Israel that we introduced are typical and meet the disease characteristics: patient age 37–51 years, textured implants, and occurring several years after implantation. All of the cases involve macrotexture implants by Allergan (one of them was Inspira, which is also a Biocell textured implant by Allergan). Late seroma was the initial presentation for all four, with no history of trauma, pain, inflammation, or physical findings. The initial workup included ultrasound evaluation for the fluid collection and histologic markers. In all of the cases, the markers were CD30 positive and ALK-1 negative, and surgical treatment included bilateral implant removal and capsulectomy. Oncology follow up was sufficient, without further adjuvant chemotherapy or radiotherapy needed.

Currently, the recent estimation is that the lifetime prevalence of the disease is 1:3817 to 1:30,000 women with a textured breast implant [3,6,7]. The last FDA update published 21 March 2018 showed a total of 414 cases worldwide, including nine deaths [6]. Based on annual sales data, we estimated that the global lifetime prevalence of the disease is 4:60,000 women with a textured breast implant or 1:15,000 women with a textured breast implant in Israel. Some patients were unilateral and we do not know how many. The total number of textured implants...
is probably even lower; therefore, we believe that the worldwide prevalence is significantly higher than past findings and we support the latest reports [3,6,7,21]. These results may be due to the fact that the cases are underreported, with lack of gathered information partly due the voluntary nature of the reports. Another explanation for the high incidence that we found in Israel may be unique due to the genetic background of the Jewish community living in Israel. Israel is a small western country with an organized health system and good oversight. Breast cancer awareness is high due to high incidence of breast cancer in Israel.

CONCLUSIONS
We described the first four cases of breast implant-associated ALCI in Israel. This small number of cases of a rare disease, in a small country shows that ALCI is not a common disease; however, based on our report (4;60,000 cases) as well as those of others, we believe that the prevalence is significantly higher then what was initially described. We emphasize the need for further research and collaboration among various countries as well as information about the disease etiology, epidemiology, and treatment to enhance the overall prognosis.

Correspondence
Dr. E. Bar-Meir
Padih Medical Center, Poriya 15, 908, Israel
email: eran@barmeir.co.il

References