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

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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). Until recently, the estimated incidence was 1:300,000 women with breast implants, while recent reports range from 1:3817 to 1:30,000.

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 4:60,000 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.

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First described in 1962, silicone prostheses 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 1:30,000 [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 preformed 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

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exam are preformed 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 ALCL in Israel. A retrospective analysis of four patients with ALCL 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 ALCL 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 ALCL 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 ALCL 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 ALCL 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 ALCL 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 ALCL 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 ALCL 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 ALCL, compared to women who do not have breast implants [6].

LIFETIME PREVALENCE OF BREAST IMPLANT-ASSOCIATED ALCL 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 ALCL

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)

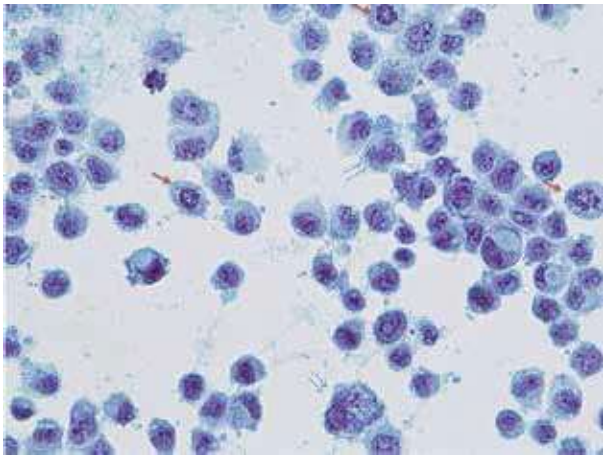

Table 1. Clinical data of the four first cases of breast implant anaplastic large cell lymphoma in Israel

	Patient 1	Patient 2	Patient 3	Patient 4
Age, years	45	51	48	37
Background	Healthy	smoker with diabetes, hypertension, and hyperlipidemia	Healthy	Healthy
Implant company	Allergan 340 gr' silicone, textured	Allergan 460 gr' silicone, textured	First surgery: Allergan, textured. Second surgery: mentor, textured	Inspira*, textured
Implant pocket	Subglandular	Subglandular	Subglandular	subpectoral
Years with implant	12	11	14	7
Late seroma	+	+	+	+
Trauma, pain, other physical findings	no trauma, no pain, no inflammation, no physical findings	no trauma, no pain, no inflammation, no physical findings	no trauma, no pain, no inflammation, no physical findings	no trauma, no pain, no inflammation, no physical findings
Pre-operation ultrasound	+	+	+	+
PET/CT exam	+	+	+	+
CD30 positive, Alk-1 negative	+	+	+	+
Surgery	Bilateral implant removal and capsulectomy	Bilateral implant removal and capsulectomy	Bilateral implant removal and capsulectomy	Bilateral implant removal and capsulectomy
Capsule pathological exam	negative	negative	negative	negative
Oncology follow up	+	+	+	+
Additional treatment	none	none	none	none
Genetic background and ethnicity	Caucasian, Jewish	Caucasian, Jewish	Caucasian, Jewish	Caucasian, Jewish

*Inspira implants are made by Allergan

Table 2. Anaplastic large cell lymphoma incidence in 2018, [Available from https://www.fda.gov/medical-devices/letters-health-care-providers/breast-implant-associated-anaplastic-large-cell-lymphoma-bia-alcl-letter-health-care-providers]

Country	Incidence of anaplastic large cell lymphoma	Implant type
Israel	1:15,000	Biocell®
United States	1:30,000	Biocell®, Siltex®
Australia	1:3345	Biocell®
	1:2832	Polyurethane
	1:86,029	Siltex®
Netherlands	1:6920	Textured implants
Canada	1:22,000	Textured implants

Biocell implants are produced by Allergan, Inamed, McGhan, CUI; Siltex by Mentor; and Polyurethane by Silimed

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 under reported, with lack of gathered information partly lost 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 ALCL in Israel. This small number of cases of a rare disease, in a small country shows that ALCL 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.

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Capsule

Specialized cutaneous Schwann cells initiate pain sensation

An essential prerequisite for the survival of an organism is the ability to detect and respond to aversive stimuli. Current belief is that noxious stimuli directly activate nociceptive sensory nerve endings in the skin. **Abdo** et al. discovered a specialized cutaneous glial cell type with extensive processes forming a mesh-like network in the subepidermal border of the skin that conveys noxious thermal and mechanical sensitivity. The authors demonstrated a direct excitatory functional connection to sensory neurons and provide evidence of a previously unknown organ that has an essential physiological role in sensing noxious stimuli. Thus, these glial cells, which are intimately associated with unmyelinated nociceptive nerves, are inherently mechanosensitive and transmit nociceptive information to the nerve.

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