Hyperstimulation of Adaptive Immunity as the Common Pathway for Silicone Breast Implants, Autoimmunity, and Lymphoma of the Breast

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Silicone, a polymeric compound, is a rubber-like material used for numerous medical purposes including dental applications, joint implants, testicular prostheses, and intraocular lenses [1]. In 1895, Vincenz Czerny, an Austrian-German surgeon [2] known as the father of plastic surgery, performed, for the first time, breast reconstruction surgery at the University of Heidelberg. Fifty years later, in 1945, women in Japan who were frequently used as prostitutes by the U.S. military, tried initially to inject goat milk and paraffin directly into their breasts, and later, industrial silicone. In 1962, silicone breast implants (SBIs) were introduced by Cronin and Gerow [2].

In this issue of the *Israel Medical Association Journal* (*IMAJ*), Ben Naftali et al. [3] described four patients, aged 37–51 years, who were diagnosed with anaplastic large cell lymphoma (ALCL) occurring 7–12 years after SBI. Three patients had Allergan plc (Dublin, Ireland) implants, whereas one had an Allergan implant in the first intervention and a Mentor implant in the second surgery. All four patients were CD30 positive and Alk-1 negative, with abnormal morphology and large anaplastic cells. They had surgical treatment with bilateral breast implant removal and capsulectomy.

According to the 1976 United States Food, Drug, and Cosmetic Act, SBIs were considered to be devices at moderate risk (class II); but, following concerns regarding their safety arising since the early 1980s, they were re-assessed as class III higher-risk devices, needing premarket approval. The U.S. Food and Drug Administration (FDA) removed all gel-filled breast implants from commercial markets, but in November 2006, approved two (Allergan Natrelle and Mentor MemoryGel) after consultations with experts and results from the manufacturer clinical studies. These two devises were approved by the FDA for breast reconstruction for women of any age and breast augmentation for women 22 years of age or older.

During the past few years, the safety of SBIs has stirred an intense, highly polarized debate, leading to contrasting positions, ranging from acritical enthusiasm to blind denial, especially concerning their potential for induction of autoimmunity. Recently, we conducted a large population-based study to assess the risk of autoimmunity in women with SBIs [4]. This study included more than 24,000 women with SBIs and approximately 100,000 age-matched controls. The study showed that women with SBIs had an increased risk of having an autoimmune disease, with an adjusted odds ratio (OR) of 1.22, 95% confidence interval 1.18–1.26, $P < 0.001$). The risk was even higher (OR > 1.5, $P < 0.05$) in certain conditions such as sarcoidosis, systemic sclerosis, and Sjögren's syndrome [4].

Other studies have shown that carrying SBIs is linked to systemic clinical symptoms reminiscent of rheumatic disorders, such as fatigue, weakness, musculoskeletal pain, morning stiffness, and dry eyes and mouth [5,6]. Moreover, it has been shown that removal of the implants can induce improvement of the silicone-related complaints in 75% of the patients [7].

The complex link between SBIs and autoimmunity can be best illustrated by the concept of autoimmune/inflammatory syndrome induced by adjuvants (Shoenfeld's ASIA syndrome), which was introduced in 2011 to gather all the autoimmune phenomena that emerged following the exposure to an adjuvant [8,9]. Indeed, based on the international registry of ASIA syndrome, in 2016 we analysed 300 cases of ASIA syndrome and found that silicone can trigger undifferentiated connective tissue disease, systemic sclerosis, and fibromyalgia [10]. Another study utilizing the same registry in its updated version with 500 cases of ASIA syndrome found that, in terms of distinct autoimmune and autoinflammatory disease associations, silicone is associated only with polygenic autoimmune disease rather than autoinflammatory disorders [11]. Taken together, these findings support the hypothesis that silicone predominantly affects the adaptive immunity rather than innate immunity.

Several plausible mechanisms have been proposed to explain the link between SBIs and autoimmune phenomena, as it has been shown in animal model studies. For

Figure 1. The chronic stimulation induced by silicone breast implants and the different phases leading to the development of silicone-related lymphomas

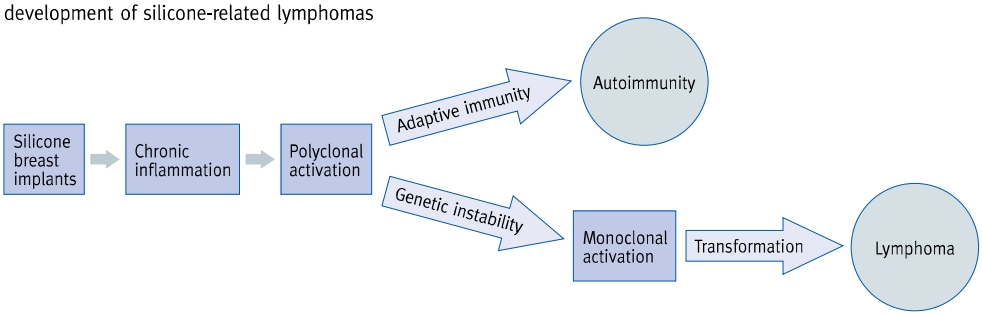

Table 1. Individuals who might be at risk for developing silicone-related autoimmune and lymphoproliferative disorders

Condition	Risks
Autoimmunity	Established autoimmune condition Significant family history for autoimmunity Known carriers of certain MHC-II alleles that are well-known to be linked with autoimmune diseases such as HLA-DR1, HLA-DR2, HLA-DRB1, and several others. Known carriers of autoantibodies
Anaplastic large cell lymphoma	Established lymphoproliferative disorder Significant family history for lymphoproliferative disorder

example, injection of silicone-gel in NZB mice has led to the induction of proteinuria and autoimmune hemolytic anemia [12], whereas implantation of silicone gel or silicone oil in MRL lpr/lpr mice has led to the increase of anti-Ds-DNA antibodies [13]

Interestingly, in a rat model study, five genes (*Fes, Aif1, Gata3, Tlr6, Tlr2*) were identified as hub genes that are most likely linked to the immune responses induced by silicone, four of which (*Aif1, Gata3, Tlr6, Tlr2*) have been linked with autoimmunity as target genes or disease markers [14]. Thus, SBIs may trigger immune responses, as various immune reactions were detected after silicone implantation.

The risk of lymphoproliferative malignancies is mainly determined by a complex interaction between genetic background, age, sex, geographic location, exposure to certain chemicals, radiation, and infections [15]. Furthermore, it has been found that patients with autoimmune disease are at higher risk to develop lymphomas, mainly of non-Hodgkin subtype. This can probably be attributed to the ongoing inflammation and chronic stimulation of the adaptive immune cells with polyclonal activation that may result in monoclonality and ultimately lead to the development of lymphoma in genetically susceptible hosts.

A growing number of reports have indicated an increased risk of lymphoma in patients with SBIs, particularly of the ALCL type [16,17]. The immune system activity and surveillance play a vital role in modulating the risk of the development of a wide range of lymphoproliferative lesions and malignant lymphomas. Indeed, chronic inflammation, immunodeficiency, autoimmunity, and infections have been recently proposed as risk factors for lymphomas [18]. The relationship between SBIs and lymphoma can be exemplified by the well-established link between Epstein–Barr virus (EBV) infection and the risk of lymphoma. The pathogenesis of EBV-associated lymphomas involves a dysregulated relationship between inflammatory and inflammation-neutralizing processes, leading to the production of radical oxygen species that can cause the impairment of critical oncogenic pathways, such as p53 that promote lymphomagenesis and eventually lymphomas [15].

Over the past few decades, silicone has been found to act as an adjuvant in contrast to what was thought for many years. Silicone particles were found to be able to infiltrate in lymph nodes, not only local but also distal ones and to enhance the antigen-specific immune reactions. Therefore, the presence of SBIs is comparable to the latent infection with EBV leading to chronic non-specific stimulation of adaptive immunity, polyclonal activation, monoclonal activation, pseudolymphoma and eventually the development of lymphoma [Figure 1].

The treatment of silicone-induced autoimmunity and ALCL is mainly given by the removal of SBIs. A study by de Boer et al. [7] showed that 63% of women with SBIs who developed a subsequent autoimmune responses experienced a significant improvement in terms of systemic symptoms, such as arthralgia, myalgia, fatigue, and neurological symptoms, during an observation period of 14 months following examination. This effect can be attributed to the fact that the removal of the nociceptive signal triggered by the adjuvant contained in the SBIs prompts a regression of the immune reaction.

CONCLUSIONS

Our recommendation is to avoid SBIs in those individuals who might be at risk of autoimmunity and perhaps also of ALCL [Table 1]. In contrast to an earlier perception that regarded silicone as a biologically inert material, women with SBIs are at higher likelihood of being diagnosed with autoimmune condition and ALCL than those without SBIs. Plastic surgeons should discuss these adverse events with women planning to undergo breast augmentation surgery.

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Capsule

An Achilles' heel for KRAS mutant tumors

Mutations in the KRAS gene drive several common and deadly cancers. Unfortunately, most mutant KRAS proteins cannot be targeted therapeutically. Because KRAS-mutant pancreatic cancers rely on the transcription factor MYC, **Blake** and co-authors screened for inhibitors that decreased MYC protein abundance. An inhibitor of the cell cycle–associated kinase CDK9 decreased MYC levels independently of KRAS signaling. This finding reveals a potential therapeutic target for patients with KRAS-mutant pancreatic cancers and perhaps also those with MYC-dependent cancers.

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Capsule

Does immunological remission, defined as disappearance of autoantibodies, occur with current treatment strategies?

Sustained disease-modifying antirheumatic drug (DMARD)-free status, the sustained absence of synovitis after cessation of DMARD therapy, is infrequent in autoantibody-positive rheumatoid arthritis (RA), but approximates cure (i.e., disappearance of signs and symptoms). It was recently suggested that immunological remission, defined as disappearance of anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF), underlies this outcome. This long-term observational study determined whether autoantibodies disappear in RA patients who achieved sustained DMARD-free remission. **Boeters and colleagues** studied 95 ACPA-positive and/or RF-positive RA patients who achieved DMARD-free remission after median 4.8 years and kept this status for the remaining follow-up (median 4.2 years). In addition, 21 autoantibody-positive RA patients with a late flare, defined as recurrence of clinical synovitis after a DMARD-free status of ≥ 1 year, and 45 autoantibody-positive RA patients who were unable to stop DMARD therapy (during median 10 years) were studied. Anti-cyclic citrullinated peptide 2 (anti-CCP2) IgG, IgM and RF IgM levels were measured in 587 samples obtained at diagnosis, before and after achieving DMARD-free remission. 13% of anti-CCP2 IgG-positive RA patients had seroreverted when achieving remission. In RA patients with a flare and persistent disease this was 8% and 6%, respectively ($P = 0.63$). For anti-CCP2 IgM and RF IgM, similar results were observed. Evaluating the estimated slope of serially measured levels revealed that RF levels decreased more in patients with than without remission ($P < 0.001$); the course of anti-CCP2 levels was not different ($P = 0.66$). The authors conclude that sustained DMARD-free status in autoantibody-positive RA was not paralleled by an increased frequency of reversion to autoantibody negativity. This form of immunological remission may therefore not be a treatment target in patients with classified RA.

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