Silicone Breast Illness as a Classical Example of Autoimmune/Inflammatory Syndrome Induced by Adjuvant (ASIA)

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Silicone breast implants have been used clinically since the 1960s for both cosmetic surgery and reconstruction. The medical society mistakenly considered silicone to be an inert material in relation to the human body and to the immune system. Throughout the years, many reports have accumulated regarding the detrimental effect of silicone implants on human health and a big debate regarding the safety of these implants has been raised. We previously conducted a large population-based study and reported that women with silicone breast implants (SBI) have a significant increased risk to develop autoimmune diseases [1].

Our group recently interviewed many symptomatic women with SBI who presented with various subjective and autonomic-related manifestations such as cognitive impairment, severe fatigue, depression, widespread pain, palpitations, paresthesia, memory loss, dry eyes, and dry mouth. Previous routine blood tests were found to be interpreted as normal in these women and unfortunately anti-depressants and anti-psychotic drugs could not help their situation and actually make it worse.

We hypothesized that dysregulation in the titter and functional activity of unique circulating autoantibodies directed against autonomic nervous system receptors might explain the panoply of clinical manifestations reported by women with SBI [2]. We found a significant change in the titters of certain autoantibodies directed against autonomic nervous system autoantigens in symptomatic women with SBI. Importantly, passive transfer of immunoglobulin G (IgG) antibodies isolated from symptomatic women with SBIs into mice brains causes depression/apathic-like behaviors in the mice (personal communication).

Overall, silicone breast illness is a classic example of autoimmune/inflammatory syndrome induced by adjuvant (ASIA) due to the chronic adjuvant activity of this non-self, silicone material that may lead to the production of classical and non-classical autoantibodies and to the development of autoimmune diseases in genetically susceptible individuals. We urge the medical community and health providers to be more aware of subjective clinical manifestations reported by women with SBI. Both clinicians and scientists should work together to find alternatives to silicone implants and to find treatments for severe symptoms reported by women with SBI and by other patients with suspected autoimmune dysautonomia-related disorders.

In the 1960s, the medical community concluded that silicone was an inert material in the human body and to the immune system, and therefore it could be used for cosmetic surgery and reconstruction of the breasts [3].

Silicone material cannot be found in nature. Silicone is a branched polymer that has been fabricated from silica atoms. It is worth mentioning that long exposure of humans to silica has been shown to trigger the development of autoimmune diseases [4,5].

Notably, few years after the first augmentation mammoplasty, Kumagai and colleagues [6,7] described the development of scleroderma and other human adjuvant diseases following silicone cosmetic surgery. The silicone material can chronically hyperstimulate the immune system and can lead to the development of an autoimmune disease in genetically predispose people, for example those with polymorphism in the human leukocyte antigen [HLA] gene [8]. In 2011, Shoenfeld and colleagues introduced the autoimmune/inflammatory syndrome induced by adjuvant (ASIA) syndrome for a group of immune-mediated complex syndromes developed in genetically predispose individuals. ASIA is associated with non-specific clinical manifestations followed by exposure of these subjects to adjuvants [9]. The adjuvant activity of the silicone has already been described in both experimental animal models and in humans [4,10-12].

Many research studies have been accumulated regarding the detrimen-

tal effect of silicone implants on human health and its association with systemic clinical manifestations, rheumatic diseases, connective tissue diseases, and cancer [10-15]. Therefore, the U.S. Food and Drug Administration (FDA) imposed a moratorium on silicone implants between 1992 and 1996. Later, the FDA allowed the use of the silicone implants as long as the companies who sold these implants provided relevant information regarding patient reports on side effects and clinical manifestations following implantations.

In reality, the companies continued to sell the silicone implants and failed to report the information required by the FDA. Reports came from all over the world regarding the development of rheumatic systemic effects. A rare type of lymphoma, namely breast implant associated-anaplastic large cell lymphoma (BIA-ALCL), in women with silicone breast implants (SBI) was reported. Therefore, the FDA imposed a boxed warning against the silicone implants in 2019 and asked healthcare providers, such as plastic surgeons and family physicians, to discuss the potential complications triggered by silicone implantation with women who planned to undergo cosmetic or reconstruction surgery.

Our group has explored the effect of silicone on human health for few decades. We found the emergence of classical autoantibodies in both asymptomatic and symptomatic women with SBI [16]. We also described that silicone can bleed and migrate outside the implants, which is consistent with other groups. Magnetic resonance imaging and computed tomography scans can show the accumulation of silicone material in lymph nodes of symptomatic women with SBI [17].

A group from the Netherlands found that silicone microparticles can migrate toward the thyroid, gut, spinal cord, and even the brain in woman who had silicone breast implants and unfortunately died from complications of breast cancer [18]. Importantly, in a large population-based study, comparing approximately 20,000 women with SBI vs. about 100,000 sex- and aged-matched healthy controls, we reported that women with SBI have a significant increased risk to develop autoimmune diseases such as Sjögren's syndrome, sarcoidosis, and systemic sclerosis [1]. Moreover, women with SBI are at a significant risk to develop rheumatoid arthritis and fibromyalgia [1].

In light of these findings, the FDA recently updated the boxed warning against SBI and stated that patients receiving breast implants have reported a variety of systemic symptoms such as joint pain, muscle aches, chronic fatigue, and autoimmune diseases.

In the last 2 years, approximately 150 symptomatic women with SBI came into our clinic at the Zabludowicz Center for Autoimmune Diseases at Sheba Medical Center, Israel. These women presented with various subjective, enigmatic, and autonomic-related manifestations including cognitive impairment, severe fatigue, depression, widespread pain, palpitations, paresthesia, memory loss, hearing abnormalities, dry eye, and dry mouth. Most of these women already had several appointments with rheumatologists and/or family physicians who could not help them with symptom relief. In fact, routine blood tests of these women were found to be normal. Some of these women had been prescribed with anti-psychotics and anti-depressants drugs. The drugs did not help the patients and actually made their clinical manifestations worst [2].

Subjective/autonomic-related manifestations reported by symptomatic women with SBI are known to be reported also in patients with other suspected autoimmune dysautonomic-related disorders such as chronic fatigue syndrome, postural orthostatic tachycardia syndrome, and fibromyalgia syndrome [19]. Moreover, the involvement of unique autoantibodies against G-protein coupled receptors (GPCRs) of the autonomic nervous system in the development and pathophysiology of these syndromes have already been described [20]. Therefore, we hypothesized that dysregulation in the titters and functional activities of anti-GPCRs autoantibodies directed against autonomic nervous system receptors might explain, at least in part, some of the subjective and autonomic-related manifestation reported by symptomatic women with SBI. Indeed, we recently reported significant changes in the titters of anti-β1 adrenergic receptor, anti-angiotensin II type 1 receptor, and anti-endothelin receptor type A autoantibodies in women with SBI, as compared with aged matched healthy women [2]. Importantly, anti-β1 adrenergic receptor autoantibody was found to significantly associate with autonomic-related manifestations such as depression and sleep disorders reported by women with SBI [2].

To evaluate the potential pathogenic effect and functional activity of the anti-GPCRs autoantibodies, we recently isolated total IgG antibodies from the sera of symptomatic women with SBI (presenting with autonomic-related manifestations such as cognitive impairment, depression, memory loss, and widespread pain) and passively transferred them into the brain of naïve mice. We found that mice that had been injected with IgGs derived from symptomatic women with SBI showed depression/apathetic-like behaviors compared to mice injected with IgG derived from healthy IgG (personal communication).

Like previous studies [13,21] we also found that symptomatic women with SBI (n=14) who decided to remove their implants reported a significant improvement in their clinical symptoms and overall health status (unpublished data).

Overall, silicone breast illness falls under the umbrella of ASIA, a cluster of related immune mediated diseases that develop among genetically predisposed subjects as a result of adjuvant agent exposure.

We urge healthcare providers such as family physicians, rheumatologists, and plastic surgeons to be more aware to the association of silicone breast im-

plants with enigmatic/subjective and neurological/autonomic-related clinical manifestations reported by their clients. It is also worth mentioning that current alternatives to silicone breast implants have been studied, including the use of autologous fat grafts for breast surgery and tissue flap surgery for breast reconstruction [22,23].

The decision in the 1960s to allow the use of silicone for breast surgery was a historical medical error. The non-self silicone material acts as an adjuvant in the human body, which can causes overactivation of the immune system to attack the implants in genetically predispose individuals. Moreover, it might trigger the production of classical and non-classical autoantibodies directed against peripheral and central autoantigens, which might lead to the development of autoimmune dysautonomia in women with SBI [2,19] and in rare cases to the development of BIA-ALCL, a rare type of T cell lymphoma. Importantly, the removal of this adjuvant might lead to significant improvement of non-specific manifestations reported by symptomatic women with SBI. Therefore, silicone breast illness can serve as a classical example of ASIA syndrome.

CONCLUSIONS

The medical community, both clinicians and scientists, must be more aware of silicone breast incompatibility syndrome and work together to find alternatives to silicone breast implants and to improve the quality of life of symptomatic women with SBI.

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Capsule

Big step forward for Parkinson's disease

Inhibition of the kinase LRRK2 has emerged as a promising disease-modifying therapeutic target for Parkinson's disease. **Jennings** et al. reported evidence that DNL201, a first-in-class central nervous system-penetrant LRRK2 kinase inhibitor, reduces LRRK2 activity and restores lysosomal function in cellular and animal models. In healthy volunteers and patients with Parkinson's disease, DNL201 inhibited LRRK2 kinase activity and demonstrated an impact on lysosomal function at doses that were safe and generally well tolerated. These findings provide support for advancing the investigation of LRRK2 inhibitors to late-stage clinical studies in patients with Parkinson's disease.

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