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REVIEW ARTICLE

Autoimmune/inflammatory syndrome induced by adjuvant (ASIA) evolution after silicone implants. Who is at risk?

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Abstract Silicone implants have been in use since the mid-twentieth century, especially in the field of reconstructive breast surgery, and have long been considered as biologically inert and harmless. However, growing body of evidence from the past two decades links silicone with subsequent autoimmunity-related complications, collectively known as autoimmune/inflammatory syndrome induced by adjuvant—ASIA. Previous data suggest that while some patients tend to develop post-exposure autoimmune phenomena such as ASIA, other do not. However, thus far, no criteria for risk stratification were suggested. This current review summarizes the data linking silicone implants and autoimmunity, suggesting means of defining individuals who are at increased risk to develop silicone-induced ASIA, and therefore, a recommendation was made to avoid silicone implantation, e.g., individuals with previously diagnosed autoimmune disorders or with genetic preponderance for hyperactive immune system should not be considered as candidates for silicone implantation.

Keywords Adjuvant · ASIA · Autoimmune disease · Autoimmune/inflammatory syndrome induced by adjuvant · Autoimmunity · Relative risk · Silicone

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Introduction

Silicone implants have been used in numerous medical prostheses and devices including joint implants, intraocular lenses, artificial heart valves, testicular prostheses, and breast implant for almost six decades [1–3]. Growing evidence over the past two decades link the mere presence of silicone implants with subsequent autoimmunity-related complications [4–9]. With the recent definition of the autoimmune/inflammatory syndrome induced by adjuvant, i.e., ASIA [10–12], silicone's role as a potential trigger for autoimmunity has been reinforced [13]. Previous data suggest that while some patients tend to develop post-exposure autoimmune phenomena such as ASIA, other do not [13]. Notwithstanding the widespread use of silicone implants and although the aforementioned risks are considerable, thus far, criteria for risk stratification were not defined. Our review summarizes the data linking silicone implants and autoimmunity. More importantly, we suggest means of identification for some groups of individuals which might be at increased risk to develop silicone-induced ASIA, defining their characteristics.

Silicone as an adjuvant in ASIA

Silicone is a group of synthetic polymers containing alternating silicone and oxygen atoms. Silicone has several potential physical presentations, including liquid, resins, and elastomers, determined by the amount of their polymerized siloxanes. Silicone's widespread commercial applications are

based on its aforementioned variations and the optimal combination of properties such as temperature stability, oxidation resistance, and assumed inertness to human body and immune system [14]. Nevertheless, myriad adverse reactions in patients with silicone implants have been described.

One such group of complications can be collectively defined as localized and include tender lymphadenopathy, skin lesions [15], and nodular foreign body granulomas. In some reports, removal of the silicone gel breast implants led to remission of these localized phenomena. Table 1 includes references to case reports and case series of both localized and systemic immunologic remission after silicone gel explantation [16].

Thomas et al. performed silicone gel-filled breast implants extraction from 25 patients who developed rheumatologic symptoms (such as arthralgia, xerostomia, fibromyalgia, etc.) after implantation. In all cases, the histopathological analysis revealed signs of peri-capsular chronic inflammation [17], suggesting that the inflammatory process was ongoing rather than temporary. In addition, the silicone's ability to diffuse, through even intact envelope, a property known as "silicone bleed" [18] can further enhance peri-capsular inflammation or lead to allergic reactions [19], potentially underlying capsular fibrosis around the prostheses.

The second and more striking interaction is of silicone implants and whole-body components of the immune system. To assess silicone's ability to mediate cellular immune response, Kossovsky et al. [20] injected medical silicone oil to guinea pigs. An intradermal antigen challenge performed a month later revealed three to four times greater induration compared to controls. Moreover, predominant lymphocytic infiltrate was found microscopically, suggesting underlying immunogenic potential of silicone. Naim et al. [21] performed a series of experiments on the effects of silicone on the immune system and found that silicone gel is capable of causing a delayed-type hypersensitivity reaction, a known cell-mediated reaction [21]. Wolfram et al. suggested that a specific antigen-driven local immune response, involving activated Th1/Th17 cells, is triggered by silicone implants. T cells around the silicone capsule tend to synthesize interleukin-17, interleukin-6, interleukin-8, and other growth factors [22]. The resultant peri-capsular fibrosis is promoted by the production of pro-fibrotic cytokines. The above phenomenon exemplifies a direct effect of silicone on cellular immunity.

Adjuvant effects on the humoral immune system are the additional facet of silicone's effect on immune system. In the experiment comparing the adjuvant effect of Freund's adjuvant vs. silicone gel in rats, the latter led to more enhanced immune response [23]. In 57 consecutive patients participating in a study from California, 35 % of women with silicone breast implants tested positive to anti-collagen autoantibodies, similar to the prevalence in patients with erosive arthritis [24]. A similar effect was shown in animal models when Schaefer et al. [25] injected silicone gel to MRL/lpr mice (murine lupus model). Interestingly, anti-DNA antibodies and IL-2 levels were significantly increased in MRL mice implanted with silicone gel compared to control animals [25]. Cuéllar et al. tested 813 individuals with silicone breast implants for antinuclear antibody (ANA) using a HEp-2 cell line. Strikingly high ANA positivity was detected (57.8 %). Of note, nuclear and anticentromere immunofluorescent patterns which are predominant in the idiopathic form of scleroderma were found in 13.3 and 1.06 %, respectively [26]. Data relating to silicone implants with resultant autoimmune-like phenomena, collectively termed "the adjuvant disease," was already introduced more than two decades ago [27]. Silicone implant incompatibility syndrome (SIIS) associating silicone exposure with myriad systemic autoimmune diseases is a related phenomenon. In an analysis of 32 consecutive SIIS patients who fulfilled ASIA diagnostic criteria, autoimmune disease and impaired humoral response was found in 17 of 32 and 15 of these 32 patients, respectively [28, 29]. A review by Lidar et al. [30] describes the proposed mechanisms by which silicone mediate autoimmunity in general as well as the evidence for a casual association between this adjuvant and specific autoimmune diseases, such as systemic sclerosis. Zandman-Goddard et al. found increased levels of 15 different autoantibodies in patients with silicone breast implants with and without signs and autoimmune-related complaints (122 vs. 86 women, respectively). Anti-SSB/La and anti-collagen II antibodies were significantly elevated in both groups and most predominant [6]. In a cohort study of almost 400,000 women with approximately 11,800 implanted patients, having silicone implants was associated with a relative risk of 1.24 (95 % confidence interval (CI), 1.08–1.41; P=0.0015) for all defined connective tissue disorders [31]. In a serologic evaluation of women exposed to silicone implants, isolated reductions in C3 and C4 levels were found [32]. In a German study of scleroderma patients, more than 78 % had previous exposure to silicate dust.

When taking into account all case reports and case series reporting systemic sclerosis, rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, Still's disease, as well as undifferentiated connective tissue diseases emerging in women who underwent silicone breast implants, a causal relationship between breast implants and autoimmune conditions could have a clinical relevance [9, 33–37].

Predisposition of autoimmunity: defining a population at risk for "silicone-induced ASIA"

Development of autoimmunity is believed to result from complex multifactorial interactions, involving both genetic predisposition and in some cases an unknown environmental trigger. In case of ASIA, the external stimuli can be usually recognized [38, 39]. Soriano et al. suggested that four groups of patients were at increased risk to develop ASIA following

Table 1 Studies and case studies documenting localized and systemic immunologic reaction to silicone with subsequent remission after silicone gel explantation

Reference	Publication type	No. of patients	Complication	Remarks
Zambacos et al. [57]	Case series	14	Silicone lymphadenopathy	Include literature review of additional 175 cases. Lymph node removal was used to exclude malignancy
Spear et al. [58]	Retrospective cohort	940	Capsular contracture	
Andrew et al. [59]	Case report	1	Silicone orbital prostheses causing nasal polyp, maxillary antral pain and infection	
Kulmala et al. [60]	Retrospective cohort	169/470 (local complications/ total cohort) women	Capsular contracture, infection, implant rupture silicone granuloma	
Siggelkow et al. [61]	Case series	53	Capsular contracture, seroma, hematoma and infection	
Kao et al. [62]	Case report	1	Silicone lymphadenopathy	Mimicking recurrence of breast cancer and indicated explantation with complete capsulectomy
Wolfram et al. [63]	Case control	143 (93 with silicone implants vs 50 controls)	Significantly increased circulating immune complexes, procollagen III, anti-polymer antibodies (APA), and soluble intercellular adhesion molecule-1 (sICAM-1)	Some patients have shown prompt remission of symptoms upon removal of the implant
Kaiser et al. [64]	Case report	1	SLE	Clinical and serologic resolution after explantation
Endo et al. [65]	Review	–	Scleroderma-like skin changes, arthritis, Raynaud's phenomenon, rheumatoid factors, and ANAs	3/8 patients improved after explantation
Thomas et al. [17]	Case series	25	Rheumatologic disorders such as mastodynia, arthralgia, fibromyalgia, xerophthalmia, xerostomia, hypesthesia, and amblyopia	Subjective improvement of patient-reported symptoms over months post-explantation
Meier et al. [66]	Case report	2	Polyarthritis after insertion of silicone breast implants	Remission after implant removal in two HLA-identical sisters
Wallace et al. [34]	Retrospective cohort	30 (post-implantation SLE)/15 (post-implantation scleroderma)	26/45 explantations	Two subjective and serologic remissions One patient developed malignant hypertension and a scleroderma renal crisis
Jara et al. [37]	Case study	1	Still's disease reactivation following silicone implants with transient lupus-like syndrome	Total remission after explantation

vaccination [11]. We believe that the following groups of patients share predisposition to development of silicone-induced ASIA as well:

1. Patients with prior documented autoimmune reaction to an adjuvant (vaccination, implant, etc.)—prevention of co-adjuvant effect

Since ASIA is considered to be a group of autoimmune responses resulting from chronic immune stimulation by adjuvants [40], it seems necessary to study previous documented reaction to an adjuvant as a risk factor for potential future reaction.

In a report by Konstantinou et al. [41], a direct causal link between leukoencephalitis episodes and hepatitis B

vaccination was suggested. Interestingly, after radiological resolution in MRI and stable neurological signs, recurrence of two similar leukoencephalitis episodes shortly after administration of the second and third doses of hepatitis B vaccine were documented in the same patients [41]. ASIA consists of several conditions, such as siliconosis, macrophagic myofascitis, the Gulf War Syndrome (GWS), as well as the sick building syndrome as a part of the autoimmune (auto-inflammatory) syndrome induced by adjuvants [42]. As individuals with previously documented adjuvant exposure-associated autoimmunity (ASIA) of any kind may potentially recur, we suggest that such individuals should be deferred from silicone implantation. In cases of patients who already bare silicone implants, we suggest consideration of implants' explantation and avoidance of re-implantation in case of either clinical or serological evidence of autoimmune processes.

2. Patients with established autoimmune conditions

   It is already known that individuals diagnosed as having any autoimmune disease are at a higher risk of developing another autoimmune disorder [43]. In accord, patients with autoimmune disorders, such as rheumatoid arthritis, are considered prone to developing autoantibodies upon presentation of exogenous adjuvants [44]. We suggest that individuals with previously diagnosed autoimmune disorders should not be considered as candidates for silicone implantation.

3. Patients with history of allergic conditions/atopic disorders

   History of atopic conditions may signify a predisposition to develop ASIA. In a Dutch cohort [45], out of 80 women who developed silicone-induced ASIA, 75 % reported preexisting allergic conditions prior to silicone implantation: 24 % had prior reported eczema, hay fever, pollen, and dust mites allergy; 17 % developed allergic reactions to different medications; 4 % had rubber or Latex allergy; and a major group of 24 % had previous allergy to multiple allergens [45]. We suggest that atopic individuals should also be considered as unsuitable for silicone implantation.

4. Individuals who are prone to develop autoimmunity (with either genetic predisposition and/or relevant environmental triggers)

   Clustering of autoimmune diseases in families is well recognized, supporting a common genetic susceptibility. Several studies have acknowledged increased tendency for development of autoimmune diseases among relatives of patients with rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, and more [46–48]. In a report by Kappel et al., three sisters developed fatigue, arthralgia, myalgia, and sleep disturbances after they underwent mastectomy with silicone implantation and reconstruction. After replacing the implants to saline-filled implants, they reported improvement of all complaints. This occurrence strongly suggests a genetically determined background to this phenomenon [29].

   Immunogenetic basis of autoimmune disorders was thoroughly described. HLA-DR4-positive patients were found to be more prevalent among cohort of patients with ANCA-associated vasculitis, especially granulomatosis with polyangiitis (Wegener's granulomatosis) [49]. Similarly, HLA-DRB1 genotype was associated with myriad autoimmune conditions [50]. In the work of Young et al., 199 women with silicone implants were assessed for association between HLA group and post implantation symptoms. Interestingly, in the symptomatic patients' group, 42 % had positive antibodies against their own B lymphocytes. With regard to HLA subclass, out of these 42 %, 81 % were found to be DR53-positive. These findings suggest that DR53 may serve as a marker for women with HLA predisposition to develop silicone-induced ASIA [51]. Additional support is provided by the work of O'Hanlon et al. in which HLA typing for DRB1 and DQA1 genes was compared between three patient groups: women who developed myositis after silicone implantation, healthy women with silicone implants, and women with idiopathic myositis who do not have silicone implants. DQA1*0102 allele was considerably more common in patients who developed myositis after silicone

Table 2 Risk factors for development of silicone-induced ASIA

Risk groups	Common examples
Prior documented autoimmune reaction to an adjuvant	Vaccines
	Implants
Established autoimmune conditions	SLE, Hashimoto, Graves, type 1 diabetes, rheumatoid arthritis, etc
History of allergic conditions/atopic disorders	Eczema, hay fever, pollen and dust mites allergy, drug allergy, and rubber or Latex allergy
Prone to develop autoimmunity (with either genetic predisposition and/or relevant environmental triggers)	HLA-DR4, DRB1, DR53, DQA1*0102
	HLA-C
	Active smoking
	Obesity

implantations compared to idiopathic myositis without silicone exposure, with OR of 2.6 (95 % CI 1.25–5.46) [52]. More importantly, the co-occurrence of type-1 diabetes and celiac disease [53] in the same patients was linked to HLA-C exemplifying both genetic predisposition as well as co-existence of two immunologic phenomena. Taken together, these associations between HLA subgroups and autoimmunity are believed to represent a hyperactive immune system with the disadvantage of autoimmunity risk in one hand and an evolutionary advantage in fighting infections, such as enteric fever [54].

In addition to the genetic predisposition, environmental factors have also been linked to autoimmunity. Smoking is an example for such association, not only for disease incidence but also as a predisposing factor for worse clinical course of disease (as with systemic lupus erythematosus and rheumatoid arthritis) [39, 55]. Obesity is an additional example of such interaction. In a comprehensive review of more than 300 articles, obesity was found to be a considerable environmental trigger contributing to both initiation and progression of autoimmune disorders [56].

Conclusion

The evidence connecting silicone breast implants and resultant ASIA are accumulating. Recognition of this association necessitates definition of those women who might harbor an increased risk for this disease. We acknowledge the fact that there might be a genetic predisposition for developing autoimmunity, whereby silicone might be the "missing link" as an environmental trigger. Since such predisposition is yet to be easily diagnosed, we suggest that in the defined groups of people at risk (Table 2), consideration should be taken prior to decision-making and the introduction of silicone implants. When applicable, patients at risk should be offered alternative implants such as saline-filled.

Disclosure None.

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