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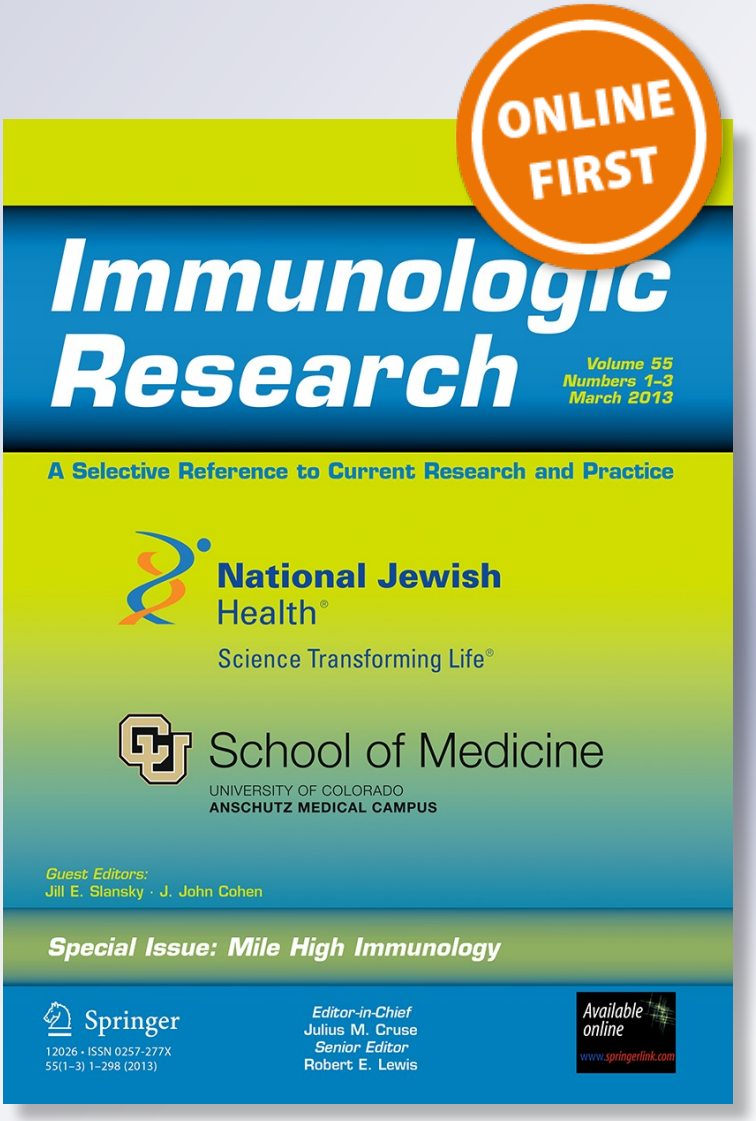

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ETIO PATHOGENESIS OF AUTOIMMUNITY

Silicone implant incompatibility syndrome (SIIS): A frequent cause of ASIA (Shoenfeld's syndrome)

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Abstract Silicon has a molecular mass of 28 daltons. In nature, silicon is found as silicon dioxide (silica) or in a variety of silicates (e.g., in talc or asbestos). Furthermore, silicon is present in silicones, polymerized siloxanes, which are often used as medical silicones in breast implants. Silicon exposure is associated with different systemic autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, progressive systemic sclerosis, and vasculitis. Remarkably, silicon in silicone-filled breast implants is considered to be safe, not increasing the risk of developing autoimmune diseases. We analyzed the impact of silicone-filled breast implants on the immune system in 32 consecutive patients attending a specialized autoimmunity clinic. All 32 patients had silicone implant incompatibility syndrome and complaints fulfilling the diagnostic criteria of ASIA (autoimmune/inflammatory syndrome induced by adjuvants). Furthermore, in 17 of the 32 patients, a systemic autoimmune disease was diagnosed, and 15 of the 32 patients had an impaired humoral immune system. Patients developed symptoms and signs after long-term follow-up, suggesting that these symptoms and signs started after implant aging and/or rupture. We postulate that silicon in silicone-filled breast implants may increase the risk of developing (auto) immune diseases and immune deficiencies.

Keywords Silicone implants · ASIA · Adjuvants · Vasculitis · Connective tissue diseases · Immunodeficiencies

Introduction

Silicon (SI) is the major constituent of the earth's crust. Si has a molecular mass of 28 daltons.In nature, silicon is found as silicon dioxide (silica, SiO_2) or in a variety of silicates (e.g., in talc or asbestos). Furthermore, silicon is present in silicones, a polymer of siloxanes $[SiO(CH_3)_2]_n$.

Exposure to silicon-containing compounds has long been recognized as dangerous for humans, especially because inhalation of crystalline silica can result in serious occupational lung fibrosis (i.e., silicosis).

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Silicon exposure is associated not only with silicosis, but also with lung cancer and chronic renal failure. Furthermore, silicon exposure is related to autoimmune diseases. Autoimmune diseases affect approximately 5–10 % of the developed world population and are a significant cause of morbidity and mortality. The etiopathogenesis of autoimmune diseases comprises a combination of genetic, immune, hormonal, and environmental factors.

One such environmental factor is silicon exposure, and in several studies, an association between exposure to silicon and diseases such as systemic lupus erythematosus, rheumatoid arthritis, progressive systemic sclerosis, and vasculitis has been demonstrated [1–4].

For instance, in patients with silicosis, the prevalence of systemic autoimmune diseases is clearly increased and an up to 25-fold increased risk of suffering from vasculitis has been demonstrated in these patients [5].

The research connecting silicon exposure to autoimmune disease goes back almost 100 years [1]. Initially,

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research focused on occupational exposure of silica in miners and various construction trade workers, and it was demonstrated that different autoimmune diseases were more frequently occurring in these people. However, non-industrial silicon exposure may also be dangerous for humans. For instance, after disasters in which major buildings are destructed, silica content in the air increases, resulting in an increased prevalence of vasculitis [6]. Not only silica is associated with autoimmunity, but also exposure to other silicon-containing compounds may increase the risk of developing autoimmune diseases, as has been demonstrated for asbestos [7].

The association between autoimmunity and silicon exposure may result in the following scenario [1]: Silicon-containing particles are captured by macrophages, resulting in entrapment within lysosomes. Subsequently, these macrophages are activated, resulting in the production of cytokines, for example interleukin-1β, reactive oxygen species (ROS), and reactive nitrogen species. In the end, this leads to apoptosis of macrophages resulting in the release of silicon-containing particles that can be taken up once again by other macrophages. Exposure to silicon-containing particles also leads to a massive production of interleukin-17 resulting in an influx of neutrophils that are activated and produce ROS and release of myeloid granular enzymes such as myeloperoxidase. Additionally, silicon-containing particles are transported to the regional lymph nodes, resulting in a pronounced adjuvant effect. Silicon-containing particles are well-known potent stimulators of lymphocytes. For instance, silica particles induce a type 2 inflammatory response characterized by increase in IgE and IgG1 and chronic activation of T cells possibly because negative regulators of T cells are dysfunctional [8] in combination with dysfunction of regulatory T cells [9]. Whether a similar scenario is operative for silicon-containing gel in breast implants is at present unknown. However, it is well known that silicones may undergo oxidization to silica and also that silicon-containing gel induces an adjuvant effect [10].

In light of the adjuvant effect of silicones, it is surprising that silicone-filled breast implants have been reported not to increase the risk of autoimmunity [11, 12]. Importantly, however, epidemiological studies in which the relationship between breast implants and autoimmune diseases was investigated mainly focused on specific disease entities within the so-called connective tissue diseases (CTDs).

Recently, Shoenfeld and Agmon-Levin recognized that different conditions linked to exposure to adjuvants resulted in similar complexes of signs and symptoms and proposed to label this condition "ASIA" (autoimmune/inflammatory syndrome induced by adjuvants) [13]. Herein, we report a series of 32 patients with silicone-filled breast implants who were referred for symptoms of incompatibility with the implants. These patients were evaluated for ASIA, immunodeficiency, and/or autoimmune diseases.

Patients and methods

All patients referred to JWCT (Clinical Immunology Clinic of the Maastricht University Medical Center, Maastricht, the Netherlands) between January 2008 and January 2012 were evaluated for the presence of breast implants. Approximately 600 patients were evaluated, and in 32 of them, breast implants were present. In order to obtain cumulative clinical details of the patients, patients were evaluated according to a protocol with emphasis on signs and symptoms of respiratory tract and abdominal, kidney, ocular, cutaneous, central nervous system, peripheral nerve, cardiac, and musculoskeletal involvement [14]. Furthermore, special attention was paid to the occurrence of recurrent infections. In addition, the following laboratory tests were performed: erythrocyte sedimentation rate, C-reactive protein, hemoglobin, leukocyte and eosinophil count, thrombocyte count, alanine aminotransferase level, serum creatinine level, antinuclear antibodies [15], anti-neutrophil cytoplasmic antibodies (ANCA) [16], IgM reumafactor [17], cryoglobulins [17], complement levels [17], anti-cardiolipin antibodies [18], and immunoglobulin levels (IgG, IgM, IgA, and IgG subclasses).

Patient classification

Patients were classified as having silicone implant incompatibility syndrome (SIIS) if they had symptoms or signs of silicone allergy, capsular contracture, and/or systemic manifestations such as chronic fatigue, arthralgia, myalgias, asthenia, and/or fever. Patients were classified as suffering from ASIA when Shoenfeld's criteria for this syndrome were fulfilled [13]. In short, four major and four minor criteria were evaluated and when either two major or one major and two minor criteria were present, the patient was considered having ASIA. Standard diagnostic criteria were used for CTDs and anti-phospholipid syndrome [17, 18]. The diagnosis of non-Hodgkin lymphoma was made on the basis of evidence of bone marrow, nodal, or extranodal lymphoproliferative disease with pathological features that were compatible with the WHO classification of neoplastic diseases [17]. Patients were classified as suffering from immune-mediated inflammatory diseases (IMIDs) according to protocol [19]. In short, patients were classified into subgroups that had disparate organ system involvement, were physiologically distinct, and presented with contrasting symptoms [19]. Patients were classified as IMID subjects in the presence of a previously diagnosed

IMID or newly discovered systemic disorder comprising the following: vasculitides, connective tissue diseases, and others. Finally, patients were classified as suffering from immunodeficiency when total IgG levels were below 6.0 g/L or as IgG subclass deficiency when total IgG was >6.0 g/L, but when either IgG1 (<4.0 g/L), IgG2 (<1.3 g/L), or IgG3 (0.4 g/L) level was decreased.

Results

Thirty-two women with breast implant were evaluated. Their age at the time of evaluation was 18–64 years (median age 49 years). All patients had silicone implant incompatibility syndrome (SIIS) and a history of silicone-gel-filled breast implants; none of the patients had a saline-filled and/or a mixed saline–hydrocellulose-filled breast implant. All patients fulfilled the diagnostic criteria for ASIA. Patients presented with arthralgias and fatigue; the period between start of complaints and implantation of silicone breast implants varied enormously. Median time between start of complaints and time of breast implant was 10 years (2–24 years). Of the patients, 20 % reported signs and symptoms already within 2 years after operation; 33 % developed signs and symptoms between 2 and 10 years after operation; 28 % between 10 and 20 years; and 19 % more than 20 years after the breast implant operation. It, generally, took also several years before the diagnosis ASIA was made: Median time between diagnosis of ASIA and breast implant was 16 years (2–40 years).

Silicone breast incompatibility and associated diseases

In 10 patients, enlarged lymph nodes were removed (Table 1). Histological examination disclosed in 2 of 10 patients a non-Hodgkin lymphoma, whereas in the remaining 8 patients, a foreign body reaction with granulomatous inflammation containing multiple giant cells suggestive of biopsy-proven silicosis was found.

Furthermore, 17 patients were classified as suffering from a systemic autoimmune disease and 7 patients from an organ-specific autoimmune disease (Table 1).

Six of the 17 patients with a systemic autoimmune disease had a CTD: 1 patient had systemic sclerosis, 1 patient systemic lupus erythematosus, 2 patients Sjogren's syndrome, and 2 patients anti-phospholipid syndrome. In addition, 6 of 17 patients were diagnosed as suffering from a systemic necrotizing vasculitis. Furthermore, one patient was diagnosed with multiple sclerosis, and four patients had a systemic granulomatous disease: either sarcoidosis ($n = 3$) or Crohn's disease ($n = 1$). Finally, 7 patients had organ-specific autoimmune diseases: Four patients had

Table 1 Serological, histological, and diagnostic findings in 32 patients with silicone-filled breast implants and ASIA (autoimmune/inflammatory syndrome induced by adjuvants)

	Age	Serology	ID	Diagnosis	Hist
1.	39	APCA	+	PA	np
2.	49	ACL	+	APS	G
3.	45	cryo	−	MC	np
4.	49	ACL/LAC	−	APS	np
5.	39	–	+	sarc	G
6.	18	–	+	Crohn	np
7.	23	IgM-Rf	+	sarc	G
8.	70	–	−	MPA	np
9.	42	ACL	+	PAN	np
10.	53	TPO	−	EGPA/HT	np
11.	46	DsDNA/ACL/SSA	−	SLE	np
12.	49	–	−	NHL	L
13.	53	–	+	NHL	L
14.	63	TPO	−	HT	G
15.	37	–	−	–	np
16.	32	–	−	–	np
17.	54	cryo	−	MC	np
18.	40	–	+	–	G
19.	64	–	+	–	np
20.	60	Scl-70	−	Scl	np
21.	41	–	+	MS	G
22.	50.	ACPA/TPO	−	PA/HT	G
23.	44	ACPA	+	PA	np
24.	37	–	−	–	np
25.	38	–	−	–	np
26.	60	–	+	sarc	np
27.	52	ACPA	+	PA	G
28.	49	–	−	–	np
29.	49	SSA/SSB	−	Sjo	np
30.	45	SSA/SSB	+	Sjo	np
31.	40	MPO-ANCA CRYO	−	GPA	np
32.	62	ACL	+	–	np

Age at diagnosis of ASIA. At the time serology was performed, the presence of an immunodeficiency (either hypogammaglobulinemia or an IgG subclass deficiency) and the presence of an autoimmune disease were established

ID immunodeficiency, *AID* autoimmune disease, *hist* examination of a lymph node, *APCA* parietal cell antibodies, *ACL* anti-cardiolipin antibodies, *cryo* cryoglobulins, *LAC* lupus anticoagulant, *IgM-Rf* rheumatoid factor, *TPO* thyroid peroxidase antibodies, *dsDNA* antibodies to double-stranded DNA, *SSA* Sjogren's syndrome antibodies-A, *SSB* Sjogren's syndrome antibodies-B, *scl-70* antibodies to scl-70, *MPO-ANCA* myeloperoxidase-specific anti-neutrophil cytoplasmic antibodies, *PA* pernicious anemia, *APS* anti-phospholipid syndrome, *MC* mixed cryoglobulinemia, *sarc* sarcoidosis, *MPA* microscopic polyangiitis, *PAN* polyarteritis nodosa, *EGPA* eosinophilic granulomatosis with polyangiitis, *HT* hypothyroidism, *SLE* systemic lupus erythematosus, *NHL* non-Hodgkin lymphoma, *Scl* systemic sclerosis, *MS* multiple sclerosis, *Sjo* Sjogren's syndrome, *GPA* granulomatosis with polyangiitis. *G* granulomatous inflammation with multiple giant cells, *L* malignant lymphoma, *np* no lymph node biopsy performed

pernicious anemia and three patients autoimmune thyreoiditis.

Fifteen of 32 patients had an immunodeficiency. In 8 of these 15 patients, hypogammaglobulinemia (total IgG <6.0 g/L) was present, whereas seven patients had an IgG subclass deficiency (one patient IgG1 deficiency, two patients IgG2 deficiency, and four patients IgG3 deficiency).

Discussion

In our study, we analyzed the impact of silicone-filled breast implants on the immune system in 32 patients attending a specialized autoimmunity clinic. All 32 patients had silicone implant incompatibility syndrome (SIIS) and complaints fulfilling the diagnostic criteria of ASIA [13]. Furthermore, in about half of the patients, a systemic autoimmune disease was diagnosed and half of the patients had an impaired humoral immune system.

Silicon exposure is associated with different systemic autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, progressive systemic sclerosis, and vasculitis [1–4, 7]. Remarkably, current literature suggests that this accounts for silicon in silica and/or silicates, but not for silicon as is found in polymers of dimethylsiloxane (breast implant silicones) [11, 12]. Our study, however, suggests that also silicon in breast implants may result in immune dysregulation and the development of autoimmune diseases.

Breast implants are placed for cosmetic or reconstructive reasons, resulting in satisfactory evaluations in most of the patients who had undergone the operation. In the Netherlands, a great majority of patients chose silicone-filled breast implants although safer alternatives such as saline-filled implants or saline mixed with cellulose are available [20].

Well-known local complications of silicone-filled implants are capsular contracture and allergic reaction. In addition, there is evidence for an increased occurrence of a rare form of non-Hodgkin lymphoma, anaplastic large T-cell lymphoma, in these patients [21]. Whether there is also an increased risk of developing autoimmune diseases has been suggested already by van Nunen et al. [22] in 1982 when he described the occurrence of CTDs in three patients with silicone-filled breast implants. Since then, many cases of CTDs occurring in patients with silicone-filled breast implants have been described (reviewed in [23]).

Importantly, epidemiological studies, however, did not disclose a dramatic increase in the occurrence of CTDs in these patients [11, 23]. These epidemiological studies, however, have severe limitations. For instance, the sample sizes in these studies are too small to show a significant result [23]. Importantly, most studies determined the risk of development of CTDs shortly after the breast implantation, which may result in false-negative results since most patients do get complaints only years after the breast implant operation as was found in our study. We postulate that the interval between implant operation and complaints is so long because silicones have to migrate out of the breasts before it results in a substantial adjuvant effect. Indeed, Brown et al. [24] reported that silicone-filled breast implant rupture in combination with the presence of extracapsular silicone was related to an increased occurrence of autoimmune diseases. Furthermore, it has been demonstrated that during long-term follow-up, most implants will ultimately rupture [25]. Another shortcoming of most epidemiologic studies is that they focus on classic CTDs ignoring other (systemic) autoimmune diseases. Indeed, in our study, only 6 of 17 patients with a systemic autoimmune disease had a classic CTD, indicating that prospective studies should be performed in breast implant patients by experienced autoimmunologists to examine the exact percentage of patients with ASIA and/or other diseases.

In our study, we found that apart from ASIA and autoimmune diseases, many patients had an immunodeficiency defined as either hypogammaglobulinemia or an IgG subclass deficiency. The finding that about half of our patients with breast implants have a humoral immunodeficiency is to our knowledge new and has not been reported before. Interestingly, however, Csako et al. [26] reported that their patients with silicone-filled breast implants had lower IgG levels when compared with age-matched controls without breast implants. Importantly, in line with this study, Wick's group found that IgG was one of the prominent proteins found among proteins absorbed to the surface of explanted silicone-filled breast implants [27]. Therefore, we postulate that decreased levels of IgG (subclasses) in our patients may have been a consequence of absorption to the breast implants. Since IgG levels were not measured before the breast implant operation, however, we cannot exclude that immunodeficiencies in our patients were already present prior to the implant operation and actually were a risk factor to develop autoimmunity. Anyhow, in patients with breast implants, silicones may stimulate the occurrence of autoimmune diseases when a dysregulation of the humoral immune response is present [28]. Further prospective studies should be performed to study the association between IgG levels and breast implant operations.

The association between autoimmunity and silicone breast implants does not mean that there is a causal relationship between the two. Recently, however, we found that after replacing silicone-filled breast implants by saline–cellulose-mixed implants, most patients reported a strong amelioration of their complaints [20]. Based on these observations, we postulate that silicones when migrated

through the shell are captured by macrophages, resulting in activation of these macrophages. Importantly, silicones now may undergo oxidation, leading to the local formation of silica [10]. Alternatively, silicones are transported to the regional lymph nodes, resulting in a pronounced adjuvant effect. Indeed, there is ample evidence that an adjuvant disease can be induced when silicones are locally injected into patients for cosmetic purposes, resulting in ASIA and various autoimmune diseases [29]. Moreover, silicon has strong binding affinity for aluminum, another well-known adjuvant implicated in ASIA [30].

An important limitation of our study is that we evaluated a group of patients who were referred to an autoimmunity clinic with complaints, whereas the number of females who have undergone such a breast implant uneventfully without any complaints is unknown.

In conclusion, we reported thirty-two cases with silicone-filled breast implants that met the criteria for ASIA. The patients developed autoimmune diseases after long-term follow-up, suggesting that the symptoms and signs started after implant aging and/or rupture. Importantly, half of our patients were found to have a humoral immune deficiency possibly due to absorption of immunoglobulins to the breast implants. We postulate that silicon in silicone-filled breast implants increases the risk of developing (auto) immune diseases. Prospective long-term follow-up studies are needed in which patients with silicone-filled breast implants are evaluated for the occurrence of ASIA, autoimmune diseases, and/or immunodeficiencies.

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