Silicone breast implants and autoimmune rheumatic diseases: myth or reality

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Purpose of review
In the present review, recent findings regarding silicone breast implants (SBIs) complicated by rheumatic autoimmune diseases are described.

Recent findings
Despite changes in the principal constituents of the silicone implants during the past 50 years, silicone remained an adjuvant that may 'bleed' and subsequently may be a chronic stimulus to the immune system resulting in similar clinical manifestations as 50 years ago. Silicones are spread throughout the body and can be detected in tissues and the central nervous system. Autoimmune/inflammatory syndrome by adjuvants (ASIA), allergies, autoimmune diseases, immune deficiencies and lymphomas occur in patients with SBIs. There is a need for adequately adjusted epidemiological studies to ascertain the frequency of these diseases. Explantation of the breast implants, however, should be advised to patients with complaints, as 60–80% of patients show an amelioration of the signs and symptoms after explantation.

Summary
SBIs are associated in a proportion of patients with complaints such as fatigue, cognitive impairment, arthralgias, myalgias, pyrexia, dry eyes and dry mouth. Silicones can migrate from the implant through the body and can induce a chronic inflammatory process. Explantation of SBI results in the majority of patients in an amelioration of the symptoms.

Keywords
anaplastic large cell lymphoma, autoimmune/inflammatory syndrome by adjuvants, explantation, immune deficiency, silicone breast implants

INTRODUCTION

The first silicone breast implants (SBIs) were performed by Cronin and Gerow in 1962 [1]. Silicone gel was wrapped in an impermeable silicone envelope developed by Dow Corning. The SBI implantation procedure was considered a success, and since then, millions of women received SBI either as a cosmetic procedure or because of postmastectomy reconstruction. Soon thereafter, local and distant complications of the SBI procedure were reported and the first case reports were published with women developing arthralgias and fatigue and sometimes an autoimmune disease [2–5]. Over the next 50 years, hundreds of patients are reported with similar symptoms and signs [6▪▪]. Both patients and doctors suspect that these complaints are caused by the implants. Indeed, removal of the SBI results in an amelioration of symptoms in 60–80% of the patients [7▪▪].

During recent years, we have seen over 200 patients with clinical signs and symptoms of this so-called silicone-incompatibility syndrome. In the current review, we describe signs and symptoms, and discuss potential pathophysiological mechanisms and disease management.

SYMPTOMS AND SIGNS

Typically, patients develop chronic fatigue and are already tired when they wake up, whereas the fatigue is not alleviated by rest. Patients have a substantial reduction in the ability to engage levels of occupational, educational, social and/or personal

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KEY POINTS

- Silicone breast implants are associated in a proportion of patients with complaints such as fatigue, cognitive impairment, arthralgias, myalgias, pyrexia, dry eyes and dry mouth.
- Silicones can migrate throughout the body and can be detected in tissues and the central nervous system.
- Migrated silicones induce a chronic inflammatory process.
- Probably due to chronic inflammation autoimmune/inflammory syndrome induced by adjuvants (ASIA), allergies, autoimmune diseases, immune deficiencies and lymphomas occur in patients with silicone breast implants.
- Explantation of the breast implants should be advised to patients with complaints, as 60–80% of patients show an amelioration of the signs and symptoms after explantation.

activities as before the illness started. Sleep disturbances such as problems falling asleep and/or staying asleep are often present. In addition, most patients report postexertional malaise. Probably related to these symptoms are the symptoms of cognitive impairment resulting in memory deficits ('Alzheimer-light'), absent-mindedness, word-finding difficulties and difficulty paying attention.

Another early symptom is the occurrence of arthralgias or arthritis that is present in more than 90% of the patients. Most patients fulfil the 2016 criteria for fibromyalgia (see Table 1) [8]. Most (70–80%) patients also suffer from morning stiffness that sometimes may last more than an hour. Patients, however, may also present with a symmetric polyarthritis compatible with a diagnosis of rheumatoid arthritis [9,10▪▪].

In addition, up to 90% of the patients have myalgias and/or muscle weakness. Weakness can be severe and may render the patient to be bedridden. In one study, an electromyography (EMG) was performed in 93 patients. The EMG was

Table 1. Fibromyalgia 2016 criteria

Criteria
A patient satisfies modified 2016 fibromyalgia criteria if the following 3 conditions are met:
(1) Widespread pain index (WPI) ≥7 and symptom severity scale (SSS) score ≥5 OR WPI of 4–6 and SSS score ≥9
(2) Generalized pain, defined as pain in at least four of five regions, must be present. Jaw, chest and abdominal pain are not included in generalized pain definition.
(3) Symptoms must have been present for at least 3 months.
(4) A diagnosis of fibromyalgia is valid irrespective of other diagnoses. A diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses.
Notes
(1) WPI: note the number of areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19.
(2) Symptom severity scale (SSS) score
Fatigue
Waking unrefreshed
Cognitive symptoms
For the each of the 3 symptoms above, indicate the level of severity over the past week using the following scale:
0 = No problem
1 = Slight or mild problems, generally mild or intermittent
2 = Moderate, considerable problems, often present and/or at a moderate level
3 = Severe: pervasive, continuous, life-disturbing problems
The symptom severity scale (SSS) score is the sum of the severity scores of the three symptoms (fatigue, waking unrefreshed and cognitive symptoms) (0–9) and the sum (0–3) of the number of the following symptoms the patient has been bothered by that occurred during the previous 6 months:
(1) Headaches (0–1)
(2) Pain or cramps in lower abdomen (0–1)
(3) Depression (0–1)
The final symptom severity score (SSS) is between 0 and 12.

Adapted from [8].

abnormal in 53% of the patients [11]. Most often, a 'myopathic' pattern was found in these patients [11].

Furthermore, two-third of the patients report pyrexia, whereas night sweats are common. Some patients additionally have strongly elevated ferritin levels and fulfil the diagnostic criteria for (silicone-induced) Still's disease [12▪].

Importantly, 75% of patients have dry eyes and/or a dry mouth. Symptoms of the dry eyes are often severe and may result in blurred vision and/or a keratitis sicca if left untreated. Sjogren syndrome A/Sjogren syndrome B (SSA/SSB) antibodies are only present in a minority of patients [5], whereas salivary gland biopsies disclose mononuclear cell infiltrates different from what can be found in Sjogren's syndrome [13,14].

Furthermore, 30–50% of the patients develop new-onset Raynaud's phenomenon sometimes with nailfold abnormalities as demonstrated by capillaroscopy suggestive of systemic sclerosis.

Another important manifestation that is present in 30–40% of patients is the occurrence of ischemic cerebral disease or a multiple sclerosis-like syndrome [5,11]. Anticardiolipin antibodies and/or lupus anticoagulant are detected in only a minority of the patients. As patients without these antibodies lack traditional risk factors for a cerebro-vascular accident, a diagnosis of seronegative anti-phospholipid syndrome is often considered [15,16].

Allergies are reported in 50–80% of the patients [17]. In most patients, these allergies are preexistent. In many cases, however, the patient report that allergic complaints had disappeared before the SBI operation and returned thereafter. Allergic complaints include sneezing, itching of the nose and eyes, red eyes, rhinorrhea, nasal congestion and postnasal drip. Furthermore, asthmatic patients may suffer from cough, wheeze and shortness of breath. Food allergies also occur and about 10–20% of the patients develop new-onset urticaria and/or quincke's oedema. A remarkable frequent finding (about 50% of patients) is metal-allergy with nickel-induced dermatitis. Furthermore, some patients present with episodic symptoms suggesting a diagnosis of mast cell activation syndrome [18,19]. Finally, some patients present with a multiple chemical sensitivity syndrome [20]. Dyspnoea in SBI patients can be a result of severe asthma, pulmonary nodules, interstitial lung disease and/or pulmonary silicone embolism [21–23]. Furthermore, 20–40% of patients suffer from severe and/or recurrent (upper respiratory tract) infections.

Breast pain, tenderness and burning sensations are occasionally present. In addition, changes in breast shape, breast asymmetry, firmness of the breasts and breast enlargement may be noticed. Lymph nodes (axillary, cervical and inguinal) are often enlarged and tender (70–80% of patients).

Cardiovascular complaints include signs of orthostatic intolerance such as dizziness, disturbed balance, irregular heartbeat and sometimes chest pain. A mitral valve prolapse and/or joint hypermobility is found in about half of the patients [24].

Twenty to forty percent of patients suffer from gastrointestinal symptoms such as abdominal pain with changes in bowel movement patterns such as found in irritable bowel syndrome. Swallowing difficulties and/or dysphagia are in most cases related to the sicca complaints.

A substantial amount of patients (10–20%) have interstitial cystitis. The skin may be painful and burning sensations ('pins and needles') suggest that (atypical) small fibre neuropathy is present [25]. A prominent livedo reticularis can be found in about 20–30% of patients, whereas mild livedo reticularis is present in another 30–40% of patients. Occasionally, tender subcutaneous nodules can be observed in the arms, legs, abdominal wall and/or elsewhere in the body. Histologically, these nodules demonstrate granulomatous inflammation (i.e. migratory silicone granulomas) [22,26]. Finally, 20–40% of patients have ill-defined skin rashes, unexplained (sometimes severe) pruritus and/or alopecia.

Laboratory findings are often nonspecific. Generally, C-reactive protein levels are normal. Angiotensin-converting enzyme and soluble interleukin-2 receptor levels are, however, in up to 50% of patients elevated. Antinuclear antibodies are present in 20% of patients, whereas various other antibodies such as SSA/SSB, anti-dsDNA, anti-Scl-70, anticardiolipin, anti-cyclic citrullinated peptide antibodies, IgM-rheumatoid factor, antineutrophil cytoplasmic antibodies and/or cryoglobulins may be found [5,6▪▪]. Furthermore, antipolymer antibodies have been described, but their diagnostic value is at present uncertain [27]. Vitamin D insufficiency and/or deficiency is a frequent finding and 20–50% of patients have decreased levels of IgG and/or IgG subclasses [5,6▪▪].

AUTOIMMUNE/INFLAMMATORY SYNDROME INDUCED BY ADJUVANTS, AUTOIMMUNE DISEASES AND ANAPLASTIC LARGE T-CELL LYMPHOMA

The symptoms described above received during the last 50 years several different names: human adjuvant disease, siliconosis, silicone incompatibility syndrome and – more recently – autoimmune/inflammatory syndrome induced by adjuvants (ASIA) [6▪▪,28]; Table 2. Others, however, state that

Table 2. Criteria for the diagnosis of autoimmune/inflammatory syndrome induced by adjuvants

Major criteria
Exposure to an external stimulus (infection, vaccine, silicone, adjuvant) prior to clinical manifestations
The appearance of 'typical' clinical manifestations
Myalgia, myositis or muscle weakness
Arthralgia and/or arthritis
Chronic fatigue, un-refreshing sleep or sleep disturbances
Neurological manifestations (especially associated with demyelination)
Cognitive impairment, memory loss
Pyrexia, dry mouth
Removal of inciting agent induces improvement
Typical biopsy of involved organs
Minor criteria
The appearance of autoantibodies or antibodies directed at the suspected adjuvant
Other clinical manifestations (i.e. irritable bowel syndrome)
Specific HLA (i.e. HLA DRB1, HLA DQB1)
Evolvement of an autoimmune disease (i.e. multiple sclerosis, systemic sclerosis)
Patients are considered to have ASIA when either two major or one major and two minor criteria are present

HLA, human leukocyte antigen.
Adapted from [28].

these patients do not suffer from a separate disease, but are merely suffering from idiopathic chronic fatigue syndrome/mylagic encephalomyelitis (CFS/ME), fibromyalgia or mass somatization [29–31].

We hypothesize that as a consequence of the immune activation, ASIA, allergies, autoantibodies, autoimmune diseases, IgG and/or IgG subclass deficiencies and finally lymphomas may develop.

ASIA was firstly described by Shoenfeld and Agmon-Levin in 2011. This syndrome assembles a spectrum of immune-mediated diseases triggered by adjuvants in persons who are genetically predisposed to it [28]. Potential triggers are silicones, injection of mineral oil or other foreign substances and/or vaccines.

In 2013, we reported 32 patients with ASIA due to silicone incompatibility syndrome [5]. Median time between start of complaints and time of breast implant was 10 years (2–24 years). Fifty-three percent of the ASIA patients had an established systemic autoimmune disease, 22% of patients had an organ-specific autoimmune disease and 47% of patients a humoral immunodeficiency (either hypogammaglobulinemia or a IgG subclass deficiency). Subsequently, many patients with self-reported symptoms were evaluated in the Netherlands [6▪▪,17]. From these, about 95% fulfilled the criteria for ASIA (Table 2). These patients all had fatigue and/or cognitive symptoms, arthralgias and/or myalgias, and sicca complaints and/or pyrexia. Seventy to eighty percent of these ASIA patients had cosmetic breast augmentation, whereas 20–30% of these patients had breast reconstruction after mastectomy for breast cancer. More than 99% of the patients were women, the remaining being (transgender) males.

At present, there are no epidemiologic studies performed to calculate the risk of ASIA in SBI patients. In the Netherlands, more than 4700 women with SBI and health issues registered themselves at a Dutch foundation for women with illness due to breast implants. Unfortunately, it is not known how many Dutch women have SBI. Importantly, however, since April 2015, data about all new patients with SBI are being collected, independently and prospectively, in the Dutch Breast Implant Registry. Clearly, more epidemiological studies on the association between ASIA and SBI are needed.

Many patients also fulfil the criteria for CFS/ME [32], fibromyalgia [9], sarcoidosis [5,33] and/or undifferentiated connective tissue disease. Furthermore, a substantial number of patients have well defined systemic autoimmune diseases such as Sjogren syndrome, antiphospholipid syndrome, rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, eosinophilic granulomatosis with polyangiitis and different other forms of vasculitis [5,6▪▪,21].

Epidemiologic evidence for an increased occurrence of these autoimmune diseases is, however, sparse [10▪▪]. In a recent meta-analysis, increased risks for rheumatoid arthritis and Sjögren syndrome were found. Importantly, the systematic review concluded that studies still do not provide conclusive evidence regarding safety of SBI. Further investigations are required to determine whether increased occurrences exist between silicone gel implants and autoimmune diseases [10▪▪].

SBI patients, however, clearly have an increased risk to develop lymphomas [34,35▪,36▪▪]. Especially, the risk to develop an anaplastic large T-cell lymphoma (ALCL) of the breast negative for anaplastic lymphoma kinase-1 (ALK-1) but positive for CD30 is strongly increased (odds ratio of 18.2).

PATHOPHYSIOLOGY OF SILICONE BREAST IMPLANTS RELATED DISEASE(S)

In the late 1940s and in the 1950s, silicones were directly injected in the breast for augmentation purposes. Injected silicones, however, did not remain at the injection site and spread through the body and induced a foreign body reaction

resulting in granulomatous inflammation [37]. Furthermore, autoimmune/inflammatory phenomena may occur.

Silicone-gel can migrate outside the outer shell after SBI rupture. Migration through an intact shell has also been demonstrated (so-called 'gel bleed'). Recently, silicone material was found in multiple organs, nervous tissue and the brain in a patient at autopsy [38▪▪].

The association between SBI and ASIA may result in the following scenario [39–41]: Silicon-containing particles are captured by macrophages, resulting in entrapment within lysosomes. Subsequently, inflammasomes are activated, resulting in the production of cytokines such as interleukin-1β. Also, reactive oxygen species (ROS) and reactive nitrogen species are produced. Subsequently, apoptosis of macrophages occurs 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 enzymes such as myeloperoxidase. In addition, silicon-containing particles are transported to the regional lymph nodes, resulting in a pronounced adjuvant effect.

In animal models, it has been shown that SBI induces an adjuvant effect [42–44] and increase the susceptibility to and/or exacerbate autoimmune diseases [45–47]. In nonsusceptible animals, however, autoimmunity could not be induced [45].

Which women susceptible are for development of SBI-related disease is at present unknown. However, several factors have been postulated [48]. Firstly, patients who are known to have (a history of) allergy and/or an established autoimmune disease are at risk. Furthermore, those who have a familial predisposition for autoimmune disease are also prone to develop symptoms after SBI. It is important to realize that not only immunogenetic (i.e. human leukocyte antigen) factors play a role in the development of SBI-induced ASIA but probably also environmental factors such as smoking and obesity [48,49,50▪].

Finally, in women with SBI, it is found that the capsule around these SBIs contain inflammatory cells that are predominantly Th1/Th17 cells, whereas regulatory T cells in the capsules are defective in suppressing these intracapsular T cells [51]. These findings suggest that the Th17/Treg balance is disturbed that may result in the development of inflammatory/autoimmune diseases [52]. Importantly, many patients with ASIA due to SBI have a humoral immune-deficiency [5] and a vitamin D deficiency [53▪▪]. These two factors also increase the risk to develop an autoimmune disease in susceptible patients [5,53▪▪]. Furthermore, the chronic inflammation by the SBI in the capsule may result in progression from polyclonal lymphocyte stimulation to monoclonal lymphocyte stimulation, which in turn will result in lymphoma formation such as ALCL [35▪].

DISEASE MANAGEMENT

Unfortunately, there are no randomized clinical trials performed on the management of women with SBI-related diseases. Also, there are no (inter)-national guidelines formulated. However, on the basis of our personal experience, some therapeutic considerations should be considered.

Firstly, vitamin D deficiency and/or insufficiency should be corrected. As vitamin D may act as a regulatory agent of the immune system [53▪▪,54,55], we prescribe vitamin D supplementation to our patients [55,56]. Secondly, triggers of immune activation should be avoided and/or treated. The patient should try to quit smoking. Furthermore, antiallergic medication should be prescribed to patients with allergic rhinosinusitis, whereas bacterial (respiratory) infections should be treated with antibiotics, especially when IgG levels and/or IgG subclasses are deficient [57]. Furthermore, for eye symptoms, preservative-free tear supplements should be prescribed.

There is ample evidence that explantation of the SBI is an important first step in the management of women with SBI-related disorders [7▪▪,17]. In our recent review, we found that 469 of 622 reported patients (75%) improved after explantation. The shorter the period is that the SBI were in place, the better the amelioration of systemic symptoms and signs following removal [58]. In patients who had already developed an established autoimmune disease, only 16% improved without additional immunosuppressive therapy [7▪▪].

Unfortunately, several women still suffer from ASIA after explantation possibly because silicones are present throughout the body [38▪▪]. There are no medications that can cure ASIA, but therapy can help reduce symptoms. Suggested medications include minocycline or doxycycline [59,60,61▪], hydroxychloroquine or corticosteroids to dampen inflammation. In addition, medication may be prescribed for symptoms due to central sensitization [62▪▪], gastrointestinal involvement [63] and/or cardiovascular involvement [64]. Finally, as in patients with fibromyalgia, a combination of drug, cognitive behavioural and exercise treatment should be considered [65,66]. Also, some patients need psychiatric consultation [67].

CONCLUSION

SBIs are associated in a proportion of patients with complaints such as fatigue, cognitive impairment, arthralgias, myalgias, pyrexia, dry eyes and dry mouth. During the last few years, the concept that these symptoms are due to an adjuvant effect of migrated silicones has been further worked-out. Due to either SBI rupture or gel-bleed, silicones can migrate through the body into tissues and the central nervous system. Furthermore, these silicones can induce a chronic inflammatory process that may ultimately result in (an increase of) allergies, autoimmune diseases, immune deficiency and/or lymphomas. Explantation of SBI results in the majority of patients in an amelioration of the symptoms. There is an urgent need to start adequately adjusted epidemiological studies and creative post-marketing surveillance to obtain better evidence which percentage of patients does develop ASIA, immune deficiency, autoimmune diseases and/or ALCL.

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Conflicts of interest

None.

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In this study, 100 patients with ASIA due to silicone implant incompatibility syndrome diagnosed in 2014 were compared with 100 historical patients with adjuvant breast disease diagnosed between 1985 and 1992. Despite changes in the principal constituents of the silicone implants during the past 50 years, similar clinical manifestations were observed in the 2014 cohort, the 1985–1992 cohort and 18 other large cohorts of patients that were reviewed. It is concluded that silicone-related disease has not changed during the last 30 years.

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Breast implant associated anaplastic large cell lymphoma (ALCL) is a rare T-cell lymphoma arising around breast implants. Public awareness has increased following a safety communication warning of the association of breast implant associated ALCL by the U.S. Food and Drug Administration in 2011. Difficulty with determining an accurate assessment of risk, including diagnosis or standardized treatment regimen has led surgeons to commonly omit preoperative discussion of this rare and frequently misunderstood cancer. A model of breast implant associated ALCL informed consent implementation and healthcare provider education are reviewed with 1-year process follow-up at a tertiary cancer centre. Breast implant associated ALCL should be included during preoperative counselling on the risks of breast implantation when obtaining informed consent. Education of healthcare professionals and provision of patient-focused materials ensures effectiveness of the informed consent process.

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An autopsy was performed in a 56-year-old woman who had been exposed to gel bleed from her SBIs for 17 years. Paraffin samples were stained with hematoxylin and eosin as well as with Modified Oil O Red. Tissues embedded in plastic were sectioned and prepared for light microscope using toluïdin blue staining for transmission electron, microscopy and energy-dispersive X-ray microanalysis to measure elemental Silicon (Si). Two types of silicone material were found in multiple tissue and brain samples of this patient. The first is a droplet-like form. EDX measurements demonstrated that the droplets are composed of elemental Si. The second is a plaque-like form; these structures are composed of elemental Si and Ti (Titanium). It is concluded that Si migration had occurred throughout the whole body.

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