Editorial

Long-term inflammatory conditions following silicone exposure: the expanding spectrum of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA)

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In 1964, silicone breast implants (SBI) were introduced in the United States market by Cronin and Gerrow. Since then, they have been used worldwide to reconstruct breast shape after mastectomy or for breast augmentation (1). Systemic effects of silicone, most notably connective tissue and autoimmune diseases have been reported since the same year of its launch to the market (2, 3).

The adjuvant effect of silicone on humoral immunity has been demonstrated in the last decades, supported by the detection of significantly higher concentrations of immunoglobulins (IgG and IgM) and anti-silicone antibodies in the sera of subjects with SBI (4, 5). The immunogenic response may be induced *via* cross-reacting with connective tissue containing glucosaminoglycans, because of their content of silicone molecules (6).

The recent definition of autoimmune/inflammatory syndrome induced by adjuvants (ASIA) included silicone-related autoimmune adverse events, namely 'siliconosis', under the umbrella of the inflammatory conditions related to adjuvant exposure (7, 8).

Silicone implant incompatibility syndrome (SIIS) has been recently added as part of ASIA, referring to symptoms or signs of silicone allergy, capsular contracture, and/or systemic manifestations such as chronic fatigue, arthralgia, myalgias, asthenia, and/or fever following SBI. (9).

In the present issue of this journal, Kappel *et al*. (10) report on three sisters carrying the BCRA-1 mutations who underwent preventive mastectomy followed by reconstruction with SBI. They developed fatigue, arthralgia, myalgia and sleep disturbances within a period of 4 years after SBI. Interestingly, antinuclear antibodies (ANA) with fine-speckled staining pattern were found in all three patients. The causal relationship between symptoms and SBI is supported by the improvement of complaints after the SBI removal and the replacement with a saline (non-silicone gel containing) breast implant in all three cases. Finally, as highlighted by the authors, the observation of SIIS in three siblings with already known genetic susceptibility, strongly suggests the involvement of genetic factors in the development of such inflammatory conditions.

Indeed, this case report came following the description in 1997 of two identical HLA sisters, both receiving SBI and subsequently developing polyarthritis and neurological symptoms, who dramatically improved following implant removal. In both patients, HLA typing revealed 3 alleles typically associated with rheumatic diseases (HLA-DRB1*0405, HLA-DQB1*0302 and HLA-DRB4*01). In one of the two cases, siliconomas in axillary and pectoral lymph nodes were also detected (11).

Although the HLA typing of the three sisters was not available, the cases described in this issue fulfill the ASIA criteria because the exposure to an external stimulus led to the appearance of arthralgia, myalgia, un-refreshing sleep and fatigue (i) as well as autoantibodies (ii) ((i) major and (ii) minor ASIA criteria, respectively); in addition, the removal of the suspected inciting agent induced clinical improvement.

The 'ASIA' syndrome: the experimental models

The main suggested physio-pathologic mechanism underlying the ASIA is based on the hypothesis that early exposure to an immunologic adjuvant sets in motion a chain of biological and

immunological events that, in susceptible individuals, may ultimately lead to the development of autoimmune and rheumatic diseases (8). Adjuvants are commonly used to boost the immune response through (i) active immunostimulation; (ii) by acting as 'carriers', being immunogenic proteins that provide T-cell help; (iii) by acting as matrix for antigens, in case of 'vehicle' adjuvants such as oil emulsions or liposomes. Nevertheless, adjuvants have been documented as inductors of autoimmunity (12, 13). To date, experimental animal models of autoimmune diseases induced by adjuvants are widely used to elucidate the mechanisms and etio-pathogenesis of these diseases. In addition, animal models as a 'proof of concept' of ASIA have been recently summarised by Cruz-Tapias *et al*. (14), who focused on rheumatoid arthritis-like disease, systemic lupus erythematosus-like disease, autoimmune thyroid disease-like disease, antiphospholipid syndrome-like disease and myocarditis.
In the current issue, Bavagant *et al*. (15) investigated the role of alum, an aluminium-based adjuvant, in the induction of Sjögren's syndrome (SjS)-like disorder in NZM2758 mice, a strain genetically susceptible to develop SjS. A persistent and significant reduced salivary gland function, as well as an increased submandibular salivary gland inflammation and ANA production were observed in mice injected with alum, in comparison to the controls treated with phosphate buffered saline (PBS). As the increasing evidence of innate immunity mechanisms that are involved in the pathogenesis of SjS and given the ability of alum to activate inflammasome pathways, the authors suggest that inflammasome activation may also play a role in induction and progression of SjS (15). Although the precise mechanisms responsible for increased sialoadenitis and salivary gland dysfunction in this model are not known, this study is the first report of SjS-like disorder in an animal model induced by alum, and it may represent one of the starting points for further investigations aiming to elucidate the role of innate immunity and immunogenic adjuvants in the pathogenesis of SjS.

With regard to silicone-related adjuvant-like activity in animal models, silicone has been shown to increase circulating levels of IL-2 in murine collagen-induced arthritis and MRL models of murine lupus; in the murine collagen-induced arthritis model, long-term (12 months) silicone implantation resulted in an increased incidence of the arthritis. Thus, it has been postulated that silicone may substitute for Freund's adjuvant and act as accelerator or aggravator of the autoimmune processes (16, 17).

Silicone: not just an 'inert' bystander

SBI consists of an outer shell filled with a gel or liquid solution. Their surfaces may vary, including the presence of a coating with polyurethane (18). Polydimethylsiloxane (PDMS) is the basic material of SBI as part of the family of polyorganosiloxanes (silicone) – a linear siloxane. PDMS is an oily and sticky liquid, with surfactant properties; its viscosity increases along with chain length expansion (19). Filler composition may comprise cyclic siloxanes (D4, D5, D6), amorphous silica, and nano- and micro-scaled particles of silica.
Recently, the European Union has classified the cyclic siloxane D4 as an 'endocrine disruptor' because of its potential toxicity directed toward the reproductive apparatus - uterus and ovaries, that may impair human fertility (20). D4 is not readily biodegradable and has a high potential to bio-accumulate in the environment (20); its pharmacokinetics, when it is delivered by the inhalation or dermal routes, is similar (21).
Silica nanoparticles have been shown to induce cytokines release and apoptosis in macrophages along with cellular necrosis in *in vitro* and *in vivo* studies (22-24). Their contamination with lipopolysaccharide (LPS) may increase the cytotoxic effect and the adjuvanticity (25). Finally, it has been shown that SBI can be a source of significant platinum exposure (26).
Silicone may be considered as 'the water in a sponge', and there is a tendency for the fluid to 'bleed'. As Kappel *et al*. (10) have underlined in their paper, gel bleeding cannot be prevented in any SBI, no matter how the implant is fabricated, and it determines the chronic stimulation of the immune system. In the study by Brown *et al*. (27) it has been observed that when silicone migrated outside the scar tissue capsule surrounding the implant, women were significantly more likely to be diagnosed with an autoimmune or connective tissue disease.
Cases of gross silicone migration even to distant locations, such as shins and ankles, have been reported. In the case of Sagi *et al*. (28) a lobular granulomatous panniculitis due to silicone migration to the shin was diagnosed following SBI rupture.
Nevertheless, the problem of bleeding is not always related to the implant rupture, whose risk increases significantly with the implant age, but also with SBI composition, because of a certain fraction of low molecular weight polymers that may leak from the implants. Small PDMS molecules can pass quite easily through the intact silicone rubber membranes (29).
Macrophages charged with polyurethane from rubbers were detected in biopsies from regional lymph nodes of patients with SBI, gathering further evidences about the chronic inflammatory process that may be continuously endorsed at the tissue-implant interface and in the fibrotic tissue surrounding the prostheses (30). This may have important consequences on the therapeutic approach to patients, who may not benefit from the implant removal in case of already occurred silicone spreading through the lymph nodes or the adjacent organs.
Thus, postponed recognition of symptoms following SBI could lead to a little improvement or even to their irreversibility when the implants are removed later (10).

Silicone and autoimmunity

In this issue of this journal, Al Aranji *et al*. (31) reported the case of a 52-year-old woman who rapidly developed systemic sclerosis (SSc) complicated with scleroderma renal crisis after the rupture of SBI. Interestingly, ruptured implants were detected four years before the re-implantation. During this time interval, the patient experienced new onset of

Raynaud's phenomenon, which became more severe after the re-implantation and, in the following months, was followed by the onset of rapidly progressive diffuse cutaneous SSc with renal crisis. The autoantibody profile showed ANA with fine-speckled staining pattern and RNA polymerase III antibody positivity, the latter being associated with high probability of developing renal crisis and with poorer prognosis in such patients. Anti-centromere and Scl-70 antibodies were negative.

The review of the literature by the same authors (31) found 57 published cases of autoimmune diseases following SBI rupture, among which the most common described was SSc in 26% of the cases. SSc was detected in 324 subjects out 10,830 subjects who had undergone SBI in the study by Hennekene *et al*. (32). This study was excluded from the meta-analyses of Janowsky *et al*. (33) who analysed the relationship between SBI and the risk of connective tissue diseases. As highlighted by Al Aranjii *et al*. (31), if the Hennekene study had been included in the Janowsky analysis the adjusted relative risk of developing connective tissue diseases would have increased from insignificant 1.01 to significant 1.3.

As a matter of fact, Levy *et al*. (34) recently observed that the larger studies on connective tissue diseases following SBI are limited because of (1) the use of medical data and self reported examinations instead of clinical examinations by trained doctors; (2) the exclusive inclusion of well-defined diagnosis of autoimmune and rheumatic diseases, neglecting the non-defined symptoms such as arthralgia, myalgia, chronic fatigue, which did not fulfill any diagnostic criteria for any recognised autoimmune disease; (3) the time period of the evaluation, which in many cases is too short, while several case reports, including the one reported by Kappel *et al*. (10) pointed to the long incubation time between silicone exposure and the appearance of clinical manifestations. Fryzek *et al*. (35) reported an average length of time between implantation and symptoms of 6 years. Thus, an accurate clinical history is mandatory in the approach to these subjects.

In this regard, Maijers *et al*. (36) recently examined 80 women with SBI and undefined systemic symptoms: fatigue, neurasthenia, myalgia, arthralgia and morning stiffness were the most frequently reported (in >50% of the population). Eleven out of 80 patients developed a total of 14 confirmed autoimmune diseases at a median time of seven years after the implantation. The symptom-free period was reported with a median of 4.5 years. When classified according to the suggested ASIA criteria (7), all women had at least two major ASIA criteria and 79% fulfilled ≥3 typical clinical ASIA criteria manifestations. 52 out of 80 had an explantation and among them, 36 reported a significant decrease of their symptoms (median follow-up period: 7 months, range 1 month to 18 years). Interestingly, 60 out of 80 (75%) of patients reported pre-existent allergy prior to implantation.

Final remarks

In conclusion, there is increasing evidence of a plausible link between silicone exposure and the appearance of full-blown autoimmune inflammatory rheumatic conditions as well as non-defined silicone associated immune-mediated phenomena. Further studies and experimental models are needed to investigate host-related and implant-related factors that might explain these phenomena, whose prevalence might be underestimated if an accurate clinical history is not collected.

HLA gene testing might be a useful tool to identify women predisposed by their HLA genotype to develop symptoms following exposure to SBI; also, allergy testing prior to the implantation may reduce the risk of local allergic reactions (3).

A diagnostic rheumatologic work-up for pre-existing autoimmune phenomena is suggested before SBI, which may help to prevent autoimmune and rheumatic adverse events in predisposed subjects, such as those with family history of autoimmune diseases or subjects already diagnosed with undefined connective tissue disease (UCTD). The risk-benefit assessment should be taken seriously in these categories when SBI is performed for cosmetic reasons.

When SBI is mandatory, a long-term follow-up is strongly recommended, especially in subjects 'at risk' of developing autoimmune rheumatic diseases. Following SBI, symptoms such as arthralgia, myalgia, and chronic fatigue should not be neglected, as they may represent the onset of ASIA and may precede the development of a full-blown autoimmune rheumatic condition.

References

1. THE AMERICAN SOCIETY FOR AESTHETIC PLASTIC SURGERY: National Plastic Surgery Statistics Editor. California: The American Society for Aesthetic Plastic Surgery, 2009
2. MIYOSHI K, MIYAMURA T, KOBAYASHI Y, ITAKURA T, NISHIJO K: Hyper-gammaglobulinemia by prolonged adjuvanticity in man: disorders developed after augmentation mammaplasty. *Jpn Med J* 1964; 2122: 9-14.
3. HAJDU SD, AGMON-LEVIN N, SHOENFELD Y: Silicone and autoimmunity. *Eur J Clin Invest* 2011; 41: 203-11.
4. GOLDBLUM RM, PELLEY RP, O'DONELL AA, PYRON D, HEGGERS JP: Antibodies to silicone elastomers and reactions to ventriculoperitoneal shunts. *Lancet* 1992; 340: 510-3.
5. ZANDMAN-GODDARD G, BLANK M, EHRENFELD M, GILBURD B, PETER J, SHOENFELD Y: A comparison of autoantibody production in asymptomatic and symptomatic women with silicone breast implants. *J Rheumatol* 1999; 26: 73-7.
6. TEUBER SS, ROWLEY MJ, YOSHIDA SH, ANSARI AA, GERSHWIN ME: Anti-collagen autoantibodies are found in women with silicone breast implants. *J Autoimmun* 1993; 6: 367-77.
7. SHOENFELD Y, AGMON-LEVIN N: ASIA – autoimmune/inflammatory syndrome induced by adjuvants. *J Autoimm* 2011; 36: 4-8.
8. PERRICONE C, COLAFRANCESCO S, MAZOR RD, SORIANO A, AGMON-LEVIN N, SHOENFELD Y: Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) 2013: unveiling the pathogenic, clinical and diagnostic aspects. *J Autoimm* 2013; 47: 1-16.
9. COHEN-TERVAERT JW, KAPPEL RM: Silicone implant incompatibility syndrome (SIIS): a frequent cause of ASIA (Shoenfeld's syndrome). *Immunol Res* 2013; 56: 293-8.
10. KAPPEL RM, COHEN TERVAERT JW, PRUIJIN GJM: Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) due to silicone implant incompatibility syndrome in three sisters. *Clin Exp Rheumatol* 2014; 32: 256-8.
11. MEIER LG, BARTHEL HR, SEIDL C: Development of polyarthritis after inserction of silicone breast implant following by remission after implant removal in two HLA identical sisters bearing rheumatoid arthritis susceptibility genes. *J Rheumatol* 1997; 24: 1838-41.
12. REEVES WH, LEE PY, WEINSTEIN JS, SATOH M, LU L: Induction of autoimmunity by pristane and other naturally occurring hydrocarbons. *Trend Immunol* 2009; 30: 455-64.
13. FAVOLINO E, FAVIA EI, DIGIGLIO L, RACANELLI V, SHOENFELD Y, PEROSA F: Effects of

Adjuvants for human use in systemic lupus erythematosus (Sle)-Prone (Nzb/Nzw) F1 mice. *Clin Exp Immunol* 2014; 175: 32-40.
14. CRUZ-TAPIAS P, AGMON-LEVIN N, ISRAELI E, ANAYA JM, SHOENFELD Y: Autoimmune (auto-inflammatory) syndrome induced by adjuvants (ASIA) – animal models as a proof of concept. *Curr Med Chem* 2013; 20: 4030-6.
15. BAVAGANT H, NANDULA SR, KAPLONEK P, RYBAKOWSKA P, DESHMUKH US: Alum, an aluminum-based adjuvant, induces Sjögren's syndrome-like disorder in mice. *Clin Exp Rheumatol* 2014; 32: 251-5.
16. SCHAEFER CJ, WOOLEY PH: The influence of silicone implantation on murine lupus in MRL lpr / lpr mice. *J Rheumatol* 1999; 26: 2215-21.
17. SCHAEFER CJ, LAWRENCE WD, WOOLEY PH: Influence of long term silicone implantation on type II collagen induced arthritis in mice. *Ann Rheum Dis* 1999; 58: 503-9.
18. SAFETY OF SILICONE BREAST IMPLANTS; INSTITUTE OF MEDICINE (US) COMMITTEE ON THE SAFETY OF SILICONE BREAST IMPLANTS; Edited by Stuart Bondurant, Virginia Ernster, and Roger Herdman. Washington (DC): National Academies Press (US); 1999.
19. FLASSBECK D, PFLEIDERER B, KLEMENS P, HEUMANN KG, ELTZE E, HIRNER AV: Determination of siloxanes, silicon, and platinum in tissues of women with silicone gel-filled implants. *Anal Bioanal Chem* 2003; 375: 356-62.
20. EUROPEAN COMMISSION: DHI Water and Environment. Study on Enhancing the Endocrine Disrupter Priority List with a Focus on Low Production Volume Chemicals. Revised Report to DG Environment. Denmark: DHI, 2007.
21. SARANGAPANI R, TEEGUARDEN J, ANDERSEN ME, REITZ RH, PLOTZKE KP: Route-specific differences in distribution characteristics of octamethylcyclotetrasiloxane in rats: analysis using PBPK models. *Toxicol Sci* 2003; 71:41-52.
22. VAN DER ZEE PARK M, LYNCH I, RAMIREZ-GARCIA S *et al*.: *In vitro* evaluation of cytotoxic and inflammatory properties of silica nanoparticles of different sizes in murine RAW 264.7 macrophages. *J Nanopart Res* 2011; 13: 6775-87.
23. WILHELMI V, FISCHER U, VAN BERLO D, SCHULZE-OSTHOFF K, SCHINS RP, ALBRECHT C: Evaluation of apoptosis induced by nanoparticles and fine particles in RAW 264.7 macrophages: facts and artefacts, *Toxicol in vitro* 2012; 26: 323-34.
24. PARK EJ, PARK K: Oxidative stress and pro-inflammatory responses induced by silica nanoparticles *in vivo* and *in vitro*. *Toxicol Lett* 2009; 184: 18-25.
25. SHI Y, YADAV S, WANG F, WANG H: Endotoxin promotes adverse effects of amorphous silica nanoparticles on lung epithelial cells *in vitro*. *J Toxicol Environ Health A* 2010; 73: 748-56.
26. MAHARAJ SV: Platinum concentration in silicone breast implant material and capsular tissue by ICP-MS. *Anal Bioanal Chem* 2004; 380: 84-9.
27. BROWN SL, PENNELLO G, BERG WA, SOO MS, MIDDLETON MS: Silicone gel breast implant rupture, extracapsular silicone, and health status in a population of women. *J Rheumatol* 2001; 28: 996-1003.
28. SAGI L, BAUM S, LIAKHOVITSKY A *et al*.: Silicone breast implant rupture presenting as bilateral leg nodules. *Clin Exp Dermatol* 2009; 34: e99-101.
29. DANIELS AU: Silicone breast implant materials. *Swiss Med Wkly* 2012; 142: w13614.
30. KATZIN WE, CENTENO JA, FENG LJ, KILEY M, MULLICK FG: Pathology of lymph nodes from patients with breast implants: a histologic and spectroscopic evaluation. *Am J Surg Pathol* 2005; 29: 506-11.
31. AL ARANJI G, WHITE D, SOLANKI K: Scleroderma renal crisis following silicone breast implant rupture: a case report and review of the literature. *Clin Exp Rheumatol* 2014; 32: 262-6.
32. HENNEKENS CH, LEE IM, COOK NR, HEBERT PR, KARLSON EW, LAMOTTE F: Self-reported breast implants and connective-tissue diseases in female health professionals. A retrospective cohort study. *JAMA* 1996; 275: 616-21.
33. JANOWSKI EC, KUPPER LL, HULKA BS: Meta-analyses of the relation between silicone breast implants and the risk of connective tissue diseases. *New Engl J Med* 2000; 342: 781-90.
34. LEVY Y, ROTMAN-PIKIELNY P, EHRENFELD M, SHOENFELD Y: Silicone breast implantation-induced scleroderma: description of four patients and a critical review of the literature. *Lupus* 2009; 18: 1226-32.
35. FRYZEK JP, SIGNORELLO LB, HAKELIUS L, FELTELIUS N, RINGBERG A, BLOT WJ: Self-reported symptoms among women after cosmetic breast implant and breast reduction surgery. *Plast Reconstr Surg* 2001; 107: 206-13.
36. MAIJERS MC, DE BLOK CJ, NIESSEN FB *et al*.: Women with silicone breast implants and unexplained systemic symptoms: a descriptive cohort study. *Neth J Med* 2013; 71: 534-40.