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*LETTER TO THE EDITOR*

# RAYNAUD'S PHENOMENON AND SCLERODERMA ASSOCIATED WITH SILICONE GEL BREAST IMPLANTS: AN EXAMPLE OF ASIA SYNDROME

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**Silicone-gel breast implants (SBI) have been widely used for breast augmentation. Although silicone is generally considered an inert substance, there has been much debate recently on its role in inducing chronic inflammation and systemic connective tissue diseases. The case of a young woman affected by Raynaud's Phenomenon (RP), worsening of vitiligo and of autoimmune thyroiditis following SBI is reported in this paper. Removal of SBI led to temporary RP remission; however, despite notable clinical improvement, nailfold capillary microscopy showed progressive microcirculatory abnormalities consistent with a diagnosis of early scleroderma. Follow-up of the patient led to the diagnosis of Systemic Sclerosis (SSc) with pulmonary hypertension. The development of SSc after SBI is described, a condition that falls into the recently recognized "ASIA" (Autoimmune/inflammatory Syndrome Induced by Adjuvants) syndrome. Nailfold capillary microscopy is a valuable tool in early SSc diagnosis, in monitoring disease activity and in establishing the risk of an aggressive course of connective tissue disease following silicone breast implantation. The relationship between silicone and the immune system requires further reports and investigation in order to determine the main individual risk factors predisposing to the wide spectrum of adjuvant-induced responses.**

Systemic sclerosis (SSc) is a heterogeneous connective tissue disease of unknown etiology characterized by autoimmune processed and vascular tissue proliferation with reactive fibrosis (1). Microvascular damage may be identified and studied early in the disease by Nailfold Capillary Microscopy (NCM), a simple, non-invasive and safe imaging technique that is thought to have diagnostic and prognostic value in the presence of RP (2). The SSc classification criteria are known to perform poorly to reach an early diagnosis.

For many years, silicone materials were considered biologically inert. Following the publication of case reports and small series of patients with development of autoimmune diseases (including SSc) after Silicone-gel breast implants (SBI) (3), many studies focused on the possible link between SBI and abnormal immune responses or induction of immune-mediated diseases.

Despite extensive research on this subject, results

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of epidemiological studies have not supported any significant increased risk of any known autoimmune disease in implanted women (4-6), as the risk might be too small to be quantified. However, the role of silicone in relation to the development of defined (such as SSc) or atypical connective tissue disease is not yet clear and is still a topic of current debate (7). Recently, Shoenfeld and Agmon-Levin described an Autoimmune/inflammatory syndrome induced by adjuvants ("ASIA"), among which silicone, and have put forward provisional diagnostic criteria (8). The case of a patient who developed SSc, fulfilling the criteria for ASIA syndrome, is described here.

*Case report*

A 42-year-old female, life-long smoker, affected by Hashimoto's thyroiditis from the age of 20 and by vitiligo (at that time presenting symmetrical partially de-pigmented areas of skin limited to the fingers and groin) was referred to our centre. There was no relevant family history of autoimmune diseases and no recent exposure to vaccination.

In April 2001, aged 33, the patient underwent augmentation mammoplasty with bilateral sub-muscular breast implants (third-generation silicone gel). No adverse effects were experienced during the following nine months. In January 2002, the patient suffered breast swelling and simultaneous appearance of paroxysmal hypothermia of the hands and feet. Within days she developed classic episodes of RP with sharply demarcated pallor of the digits followed by cyanosis and erythema in response to cold temperatures, smoking and emotional stress. No action was taken to diagnose and treat the syndrome at that time.

In May 2002, surgical capsulotomy was carried out to remove the fibrous scar which had developed around the deformed, distorted breasts.

Breast discomfort and swelling was reduced for only a few days after the operation whereas RP worsened notably. Puffy hands appeared, with tenderness and swelling of the digits; at the same time the patient noted progressive extension of the vitiligo.

On initial referral to our Centre in July 2002, the patient complained of continuous, occasionally painful RP (up to 50 times a day, even in hot weather), with progressive skin involvement with swelling and thickening of digital skin. At the same time, her breasts began to harden and she suffered renewed discomfort.

Ultrasound assessment revealed a worsening of the thyroiditis. Evidence of worsening hypothyroidism with marked increases in TSH and in titer of thyroglobulin and thyroperoxidase antibodies was also revealed by laboratory tests. Autoimmune blood tests revealed antinuclear antibodies (ANAs) on Hep-2 cells in a titer of 1:640, with a nucleolar fluorescence pattern, which had previously resulted negative. Other auto-antibodies including anti-ds-DNA/RNP/SSA/SSB, anti-Scl70 and anti-centromere were negative.

NCM was performed, showing preserved capillary architecture and density. However, a number of homogeneously enlarged loops or mega-capillaries were observed in normal hairpin-shaped capillaries (Fig. 1A). The patient was prescribed oral corticosteroids and nifedipine calcium channel blocker. No positive effects on RP or digital puffiness were noted.

A further NCM performed three months later showed tortuous and irregularly enlarged loops, micro-hemorrhages, moderate loss of capillaries and moderate architectural disorganization of the micro-vascular nailfold bed. Frequent giant capillaries were also found, consistent with classic "scleroderma pattern" (Fig. 1B). Vitiligo progressed to the wrists and face.

In April 2003, due to persistent breast discomfort and to achieve improvement in the underlying systemic inflammatory syndrome, as previously described by Vasey et al., the patient opted for surgical removal of the SBI. Histological examination of the fibrous tissue around the implants revealed soft connective tissue focally infiltrated by lymphocytes and multinucleated cells and covered by fibrin on its inner side. An improvement in RP frequency and a reduction of the edema of the hands were observed following removal and after a treatment course that started with prednisone 1 mg/kg/day (Fig. 2). A slight reduction of pericapillary edema, no hemorrhages, no neo-formation of capillaries but a persisting "scleroderma pattern" were revealed by NCM (Fig. 1C); these abnormalities, linked to an underlying connective tissue disease, were closely followed-up. During the first year, a reduction of RP was seen

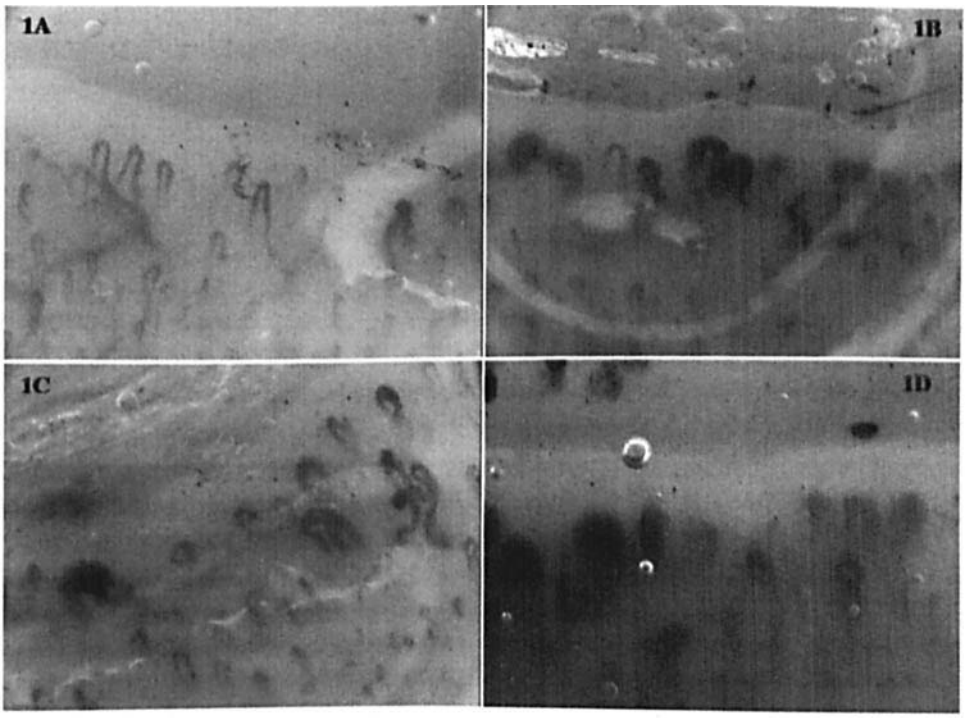


**Fig. 1.** *A) Aspecific pattern (RP). B) Scleroderma pattern. C) Improvement after surgical removal of implants (Scleroderma slow pattern). D) Scleroderma active pattern.*

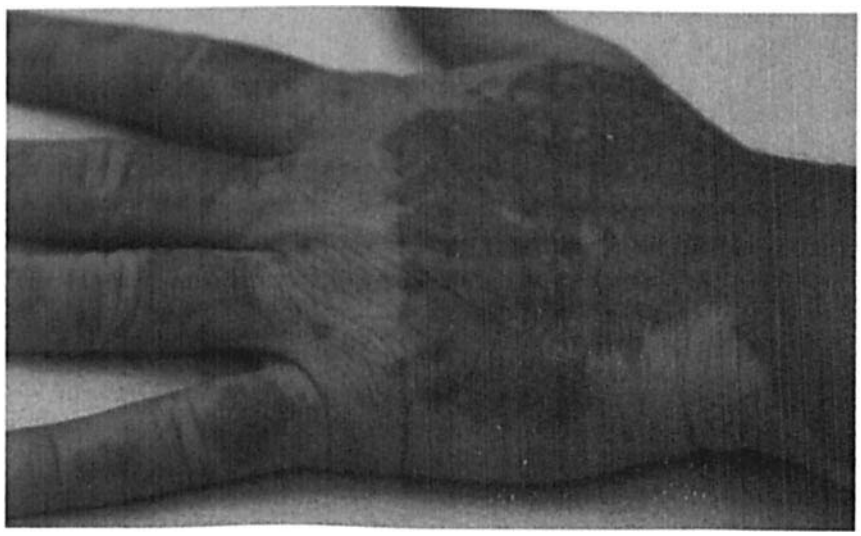

**Fig. 2.** *Patient's left hand after surgical removal of the SBI.*

without therapy, but progressive deterioration of the micro-vascular bed over time, with an "active" scleroderma pattern was observed with NCM (Fig. 1D).

At present, 9 years after implant removal, recurrence of RP has been observed and treatment with monthly Iloprost infusions with elastomeric pump is ongoing. Skin tautness and digital puffiness have slowly improved and the patient is currently affected by limited sclerodactyly and perioral

fibrosis. She has mild dysphagia and heartburn due to oesophageal involvement. Pulmonary function tests are altered, including a reduced diffusing lung carbon monoxide capacity to 65% and a mild restrictive lung disease. Echocardiography revealed an increase in systolic pulmonary arterial pressure (sPAP: 38 mmHg) rising during exercise to a maximum of 58 mmHg, while thoracic CT scan showed moderate fibrosis of lung bases. A partial repigmentation of vitiligo areas at a perioral and wrist level has been observed. Patient HLA is DR11-DQ7.5 (DQA1 0505-*0505, DQB1 0301-*0301); the presence of antibodies directed to silicone could not be tested.

## DISCUSSION

For many years silicone materials were considered biologically inert, but acting as a foreign body they elicit a granuloma formation that represents a natural host response to wall off foreign substances. It has been shown that silicone (and/or its by-products) can induce an intense local immune response, mediated by macrophages, giant cells and T lymphocytes (9). Contraction of the surrounding capsular tissue or clinically silent ruptures, that represent the vast majority of ruptured implants (10), can lead to gel leakage. Evidence of migration to other body tissues has been reported (11), even in the absence of rupture. The concept that silicone is immunologically inert has been subsequently challenged by different observations showing the development of anti-silicone antibodies in blood and tissues (12), the emergence of various auto-antibodies (6, 13) and by data suggesting a significant association between extra-capsular silicone from ruptured SBI and fibromyalgia (10). Various silicone-induced mechanisms that might act as an adjuvant (14, 15) and interact in the pathogenesis of immune-mediated disorders have been proposed (16).

In 2011, Shoenfeld and Agmon-Levin proposed the Autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA), which includes siliconosis in its spectrum, also explaining a cohort of prominent "non-defined" symptoms and signs which are linked to exposure to adjuvants (8).

In view of this, we describe a patient who developed SSc and other features that fall into the category of the recently recognized ASIA syndrome. We observed the appearance of ANAs following exposure to silicone stimulus and the evolution of a defined autoimmune disease (early SSc), together with a strong tissue response to silicone implants. Additionally, spreading of pre-existent vitiligo and worsening of thyroiditis were also witnessed. The removal of the silicone implants led to improvements in RP and in the edema of the hands, and subsequently to a slow spontaneous repigmentation of some vitiligo patches.

Considering the simultaneous occurrence of capsular contracture and early signs of SSc, supported by the serological and capillaroscopic findings, we believe that a trigger on scleroderma development by the "adjuvant effect" is what was experienced by our patient.

A local inflammatory reaction related to the physical presence of the antigenic stimulus as well as a "worsening effect" on the pre-existing autoimmune diseases (HT, Vitiligo) and on the appearance of a connective tissue disease were induced by the implants.

To our knowledge, this is the first case of SSc following silicone breast implants, the evolution of which has been documented using NCM, to be reported in literature. The presence of the capillaroscopic abnormalities is of great relevance for early SSc diagnosis. The appearance of giant capillaries and hemorrhages in a patient with RP indicates the likely presence or a higher risk of SSc development (17).

Of special interest is the progressive deterioration of the nailfold vascular bed over 20 months of apparently good health. The initial examination revealed enlarged loops or megacapillaries: this aspecific picture may be compatible with secondary RP. The second examination showed tortuous and irregularly enlarged loops, microhemorrhages, moderate loss of capillaries and moderate architectural disorganization of the microvascular nailfold bed with frequent giant capillaries. Microvascular involvement appeared rapidly progressive, with progressive capillary enlargement, giant loops and avascular areas, that are classic abnormalities of the active scleroderma pattern.

As a result of the presence of RP, autoantibodies (ANAs) and the capillaroscopic pattern, diagnosis of early scleroderma was possible. Recent literature

focuses on these signs in the diagnosis of very early SSc (18). In this case the appearance of SSc-specific ANAs could not be detected, a condition that was reported in 8-11,9% of SSc patients (19). The ANA staining pattern detected in our patient by IIF could suggest a specificity against nucleolar proteins such as anti-Th/To, anti-U3RNP, anti-PM-Scl or anti-RNA polymerase. It has been reported that genetic factors are associated with ANAs specificities, with particular reference to HLA class II. In Caucasian SSc patients, HLA-DRB1*1104 and HLA-DR11 haplotype were recently confirmed to be significantly overrepresented, in particular in those with Scl70 antibodies (19). Taking into account the homozygosity of HLA-DRB1*11-DQA1*0505-DQB1*0301 of the patient, the absence of the classic SSc antibodies could also be explained by the production of an alternative autoantibody due to the different trigger mechanism linked to silicone exposure, or for example by a HLA-mediated mechanism, independent from antigen presentation (20). Apart from patients with macrophagic myofasciitis (21), an extensive analysis of HLA in subjects developing ASIA syndrome or adjuvant diseases is lacking at present, but would be of great interest.

*Conclusion*

This case is another example of the complex interrelationship between silicone and host immune response, as there is an undisputable temporal sequence of events which led to local response, worsening of pre-existing organ specific autoimmune diseases and evolution of a defined autoimmune disease (SSc). Considering this, together with the improvement (albeit transient) in RP following surgical removal of the implants and in vitiligo, the diagnosis of SSc induced by silicone in the course of ASIA syndrome was reached.

We would like to underline the need for long term follow-up of patients who undergo SBI, and the role of NCM assessment in the presence of RP to diagnose early scleroderma. Due to the relevance of NCM also in different connective tissue diseases or inflammatory diseases, its use in suspected cases of ASIA may deserve further investigation.

Even if a link between silicone breast implants and the risk of developing a connective tissue disease cannot be strongly supported on the basis of one individual case, in agreement with most recent literature (7, 22), we would like to underline the possibility of an increased risk for a development or for a worsening of autoimmune diseases after exposure to adjuvants.

In our opinion, patients already affected by autoimmune diseases should be fully informed of the risk of a silicone implant. A genetic predisposition to autoimmunity could also imply a higher risk of an abnormal immune reaction to the antigenic stimulus of silicone. Polygenic or HLA-dependent factors may have an important role in these events.

Early diagnosis and reporting of such cases of ASIA syndrome may help to increase awareness and lead to a better understanding of the many facets of this important clinical entity.

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