ASIA Syndrome Following Breast Implant Placement

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Autoimmune/inflammatory Syndrome Induced by Adjuvants (ASIA) syndrome was first described in 2011 by Shoenfeld and Agmon-Levin [1]. The syndrome incorporates several conditions linked to previous exposure to an adjuvant substance, including silicone. It is currently still being debated whether silicone-filled breast implants increase the risk of autoimmunity. Patients develop both non-specific and specific manifestations of autoimmune diseases that cannot be classified as classic connective tissue disorders. The clinical manifestations are highly heterogeneous. Systemic autoimmune adverse reactions related to silicone have rarely been reported.

We present two cases of ASIA syndrome associated with silicone breast implant rupture. The amount of time that elapsed between silicone breast implant placement and the onset of symptoms was approximately 2 years in both cases. This time frame is consistent with the current literature, which suggests that a long interval between implant surgery and onset of symptoms (i.e., from 1 month to 39 years) is needed before observing any significant adjuvant effects by silicone migrating out of the implants.

Only a few studies have provided a detailed evaluation of the effect of silicone prosthesis removal following the development of systemic manifestations. Maijers and colleagues [2] reported that 36 out of 52 women showed a significant decrease in symptoms following an explant. In 9 of the 36 cases, symptoms had completely disappeared. Other retrospective studies also reported that removing the implants resulted in an improvement in symptoms such as fatigue, arthralgia, myalgia, sicca, and pyrexia in most patients. However, in other cases, improvement in the disease course was seen with medical treatment alone [3-4].

Recently, Dagan and co-authors [3] suggested that medical treatment alone should be the first approach. If the patient fails to recover with medical treatment, she should be provided with up-to-date information to help her decide whether to explant. Both of our patients received the most up-to-date information about their condition, and one patient decided to remove the implants while the other decided not to. Both of them showed good overall clinical response.

PATIENT DESCRIPTION

CASE 1

A 23 year old Caucasian woman underwent bilateral breast implant surgery in 1998 for cosmetic reasons.

In 2000, at the age of 25 years, she developed membranous nephropathy (biopsy-proven) that was treated with corticosteroids alone, resulting in complete remission.

Nine years later (2009) the nephropathy relapsed. She was treated with a conventional regimen of steroids with alkylating agents, again resulting in complete remission.

Over the following years the patient had two episodes of acute renal failure and worsening of proteinuria. Following the first episode, she underwent hemodialysis in another hospital and received three methylprednisolone pulses followed by oral steroids. For the second episode, she was referred to our center and given a rescue therapy combining methylprednisolone (3 bolus doses of 15 mg/kg followed by oral prednisone, 50 mg for 2 weeks, which was rapidly tapered to 5 mg in 2 months) with cyclophosphamide (two pulses of 500 mg, 2 weeks apart) in conjunction with rituximab (4 weekly doses of 375 mg/m^2). Renal function improved (SCr 1.2 mg/dl) and proteinuria dropped to < 1 gr/day.

In August 2015, the patient started to experience systemic symptoms and both her general condition and renal function worsened. A kidney biopsy confirmed the previous diagnosis of membranous nephropathy. Dialysis and administration of low doses of corticosteroids were resumed. Due to persistent arthralgia and recurrent episodes of fever that did not respond to intravenous antibiotic therapy, in December 2015, she was hospitalized for further examinations. On admission, the patient presented with a temperature of 38–38.5°C with no evidence of infection, albeit with arthralgias/knee arthritis and severe non-hemolytic anemia. Microbiology tests were persistently negative and C-reactive protein (CRP) was within normal ranges (0.5 mg/dl, cut-off value < 0.5 mg/dl), but the erythrocyte sedimentation rate (ESR) was high (86 mm/h, cut-off value 15/h). Immunological screening revealed only weak positive (1:80) antinuclear antibodies (ANA). Anti-centromere, anti-SSA/Ro, anti-SSB/La, anti-Scl70, anti-Jo-1, anti-Sm, and anti-dsDNA antibodies were negative, as were rheumatoid factor C3 and C4. Screening for fever of unknown origin and tests for familial fevers were negative. Chest X-ray, abdominal ultrasound, total body positron emission tomography (PET), and echocardiography were negative. Due to her implants, a breast ultrasound was performed. The results showed abnormalities at the margins of the prosthesis (right side)

and periprosthetic fibrosis, although with no clear signs of rupture. A breast magnetic resonance imaging (MRI) revealed the presence of intra-capsular prosthesis rupture [Figure 1A]. Symptomatic treatment with indobufen and colchicine was started, which resulted in a partial response. The fever disappeared after administering medium-high doses of corticosteroids. A further discussion of the case led to the diagnosis of ASIA as the patient fulfilled the criteria set for the syndrome, including fever, the presence of autoantibodies, chronic fatigue syndrome, muscle weakness, arthralgia, and arthritis. Based on the diagnosis, the indication was to remove the prostheses, and the patient chose to undergo the procedure. Over the following months, the fever disappeared and she reported a significant improvement in systemic symptoms and complete resolution of arthralgia.

CASE 2

A 36 year old Caucasian woman underwent bilateral mastectomy for mammary carcinoma in 2002. Since the sentinel lymph node histology examination was negative, hormonal therapy alone with tamoxifen and triptorelin was started. When she was 46 years of age, breast reconstruction using silicone prostheses was performed.

In 2014, 2 years after the surgical procedure, at age 48 years, the patient presented with acute pain on the right side of her face, which resolved spontaneously within a few days. One week later, she started to experience low back pain with lower limb irradiation that was not responsive to medium-high doses of corticosteroids (prednisone 50 mg/day) combined with symptomatic treatment with oxycodone/naloxone.

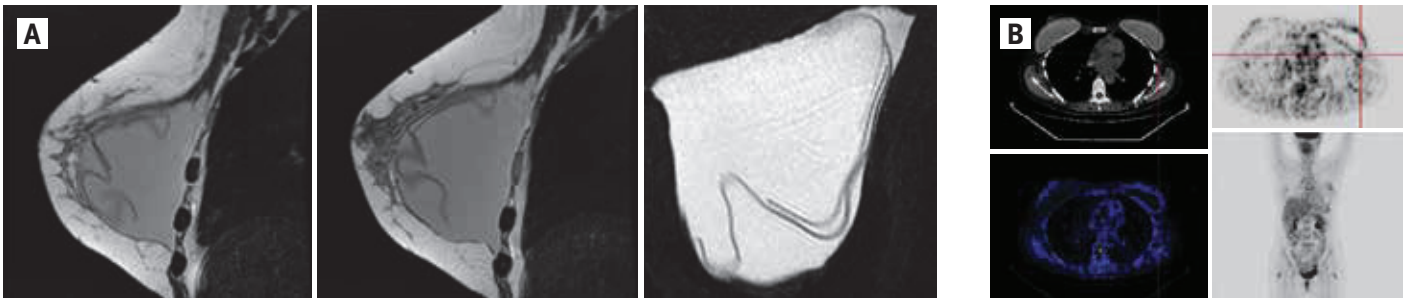
In September 2015, bone scintigraphy was performed and showed the presence of diffuse cervical-dorsal-lumbar arthritis. Based on the persistence of acute pain and the radiologic findings, the patient was hospitalized for further examination. Laboratory tests revealed an increase in both CRP levels (37.8 mg/dl, cut-off value 0.5 mg/dl) and high ESR rate (21 mm/h, cut-off value 15 mm/h). Total spine MRI revealed the presence of bilateral alterations of the trabecular bone of the clavicle and of the sternal manubrium at the level of the sternoclavicular joint due to intraosseous edema. Moreover, total body PET showed diffuse fixation of the tracer predominantly near the left prosthesis and focal hyper-fixation corresponding to multiple mammary lymphadenopathies [Figure 2B]. An ultrasound-guided breast biopsy was performed to characterize the lesions that had previously been observed in the PET. Histological results showed the presence of frustules of connective muscles with areas of fibrosis and giant cell histiocytic reaction. Mammary ultrasound revealed that the prostheses appeared to be undamaged. One month later, the patient was referred to our center because of the persistence of back pain, myalgia, and chronic fatigue syndrome characterized by the presence of severe asthenia, muscle weakness, irritability, and sleeping disorders. On admission, the physical examination was unremarkable. Serological evaluation and laboratory tests showed a normal blood cell count. Blood chemistry and urine analyses were within normal ranges. The autoimmune profile, including antinuclear antibodies, anticentromere, anti-SSA/Ro, anti-SSB/La, anti-Scl70, anti-Jo-1, anti-Sm, anti-dsDNA, and rheumatoid factor were negative. Inflammatory indices were within normal ranges. Based on these results, close follow-up alone was proposed, together with the continuation of symptomatic treatment (oxycodone/naloxone 5 mg/day and ibuprofen 600 mg as needed).

Further discussion of the case led to the diagnosis of ASIA syndrome as the patient fulfilled the criteria set for the syndrome, including exposure to an external stimulus prior to clinical manifestations and the appearance of symptoms like chronic fatigue syndrome, myalgia, muscle weakness, arthralgia, and arthritis. Therefore, on this basis, the indication was removal of the prostheses. However, the patient opted not to undergo the procedure at that time. In August 2015, she reported a spontaneous improvement in symptoms, so she stopped taking medication and was able to engage in regular physical activity.

COMMENT

Our two cases fulfilled Shoenfeld's criteria for the diagnosis of ASIA [1]. However, the type of clinical symptom presentations are unusual. Renal failure has been described in the literature. The main pathophysiological mechanism of kidney damage seems to be granulomatous inflammation confined

Figure 1. [A] Magnetic resonance imaging shows the intra-capsular rupture of the right prosthesis, **[B]** Total body positron emission tomography (PET) shows diffuse fixation of the tracer predominantly near the left prosthesis and focal hyper-fixation in correspondence to the adenopathies of the right internal mammary chain (maximum diameter 17 mm) and of the left internal mammary chain, although lower down (maximum diameter 12 mm)



to the tubule-interstitial compartment, but interstitial and membranous nephritis without any evidence of granuloma has been reported as well [2]. Following several courses of glucocorticosteroids and immunosuppressants, patient 1 chose to have the breast implants removed, while patient 2 chose not to. Both of them had good overall clinical response.

While the optimal choice still remains to be defined, clinicians should warn patients that after getting silicone breast implants, they may present with various, and more often non-specific, symptoms. When attempting to establish whether the complaints may be related to the silicone breast implants, it is important to rule out other diseases. In an attempt to relieve these symptoms, removal of the implants has frequently been indicated. Recently, De Boer et al. [2] reviewed the existing literature addressing the effectiveness of implant removal as an effective option for patients with symptoms. Removal of the silicone breast implant appeared to be effective in about 75% of patients and autoimmune diseases improved in approximately 56%. However, removal had to be combined with immunosuppressive therapy in most patients. Nevertheless, patients should be informed of the possible consequences of the surgery, including body deformity and impaired body image, which may have a significant psychological impact. Patients should also be informed of the possibility of breast reconstruction after removal [5].

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References

1. Shoenfeld Y, Agmon-Levin N. 'ASIA' – autoimmune/inflammatory syndrome induced by adjuvants. *J Autoimmun* 2011; 36: 4-8.
2. 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.
3. Dagan A, Kogan M, Shoenfeld Y, Segal G. When uncommon and common coalesce: adult onset Still's disease associated with breast augmentation as part of autoimmune syndrome induced by adjuvants (ASIA). *Clin Rheumatol* 2016; 35:1643-8.
4. Montalto M, Vastola M, Santoro L, et al. Systemic inflammatory diseases and silicone breast prostheses: report of a case of adult still disease and review of the literature. *Am J Med Sci* 2004; 327: 102-4.
5. De Boer M, Colaris M, van der Hulst RRWJ, Cohen Tervaert JW. Is explantation of silicone breast implants useful in patients with complaints? *Immunol Res* 2017; 65 (1): 25-36.

Capsule

Genetically engineered human cortical spheroid models of tuberous sclerosis

Tuberous sclerosis complex (TSC) is a multisystem developmental disorder caused by mutations in the *TSC*1 or *TSC*2 gene. Their protein products are negative regulators of mechanistic target of rapamycin complex 1 signaling. Hallmark pathologies of TSC are cortical tubers, which are regions of dysmorphic, disorganized neurons and glia in the cortex that are linked to epileptogenesis. To determine the developmental origin of tuber cells, **Blair** and colleagues established human cellular models of TSC by CRISPR-Cas9-mediated gene editing of *TSC*1 or *TSC*2 in human pluripotent stem cells (hPSCs). Using heterozygous *TSC*2 hPSCs with a conditional mutation in the functional allele, the authors showed that mosaic biallelic inactivation during neural progenitor expansion is necessary for the formation of dysplastic cells and increased glia production in three-dimensional cortical spheroids. These findings provide support for the second-hit model of cortical tuber formation and suggest that variable developmental timing of somatic mutations could contribute to the heterogeneity in the neurological presentation of TSC.

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Capsule

Combination therapy with anti-HIV-1 antibodies maintains viral suppression

Individuals infected with human immunodeficiency virus (HIV)-1 require lifelong antiretroviral therapy because interruption of treatment leads to rapid rebound viraemia. **Mendoza** and colleagues reported on a phase 1b clinical trial in which a combination of 3BNC117 and 10-1074, two potent monoclonal anti-HIV-1 broadly neutralizing antibodies that target independent sites on the HIV-1 envelope spike, was administered during analytical treatment interruption. Participants received three infusions of 30 mg/kg^{-1} of each antibody at 0, 3, and 6 weeks. Infusions of the two antibodies were generally well-tolerated. The nine enrolled individuals with antibody-sensitive latent viral reservoirs maintained suppression for between 15 weeks and more than 30 weeks (median of 21 weeks) and none developed viruses that were resistant to both antibodies. The authors concluded that the combination of the anti-HIV-1 monoclonal antibodies 3BNC117 and 10-1074 can maintain long-term suppression in the absence of antiretroviral therapy in individuals with antibody-sensitive viral reservoirs.

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