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SPECIAL TOPIC
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Three Case Reports of Adult-onset Still Disease Associated with Breast Implantation

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Summary: Autoimmune syndrome induced by adjuvants (ASIA) is an uncommon clinical condition reported by Shoenfeld et al. Although this syndrome is not scientifically validated, numerous reports on it have been published, and the manifestations are postulated to be diverse, including generalized symptoms such as chronic fatigue, myalgia, arthralgia, or dry mouth, induced by exogenous substances, specifically adjuvants, which can encompass vaccines, organisms, and silicone. Concurrently, adult-onset Still disease (AOSD) is also an infrequent ailment, characterized by spiking fever, arthritis, skin rash, lymphadenopathy, and serositis. Although the precise pathogenesis remains incompletely understood, some case reports suggest that ASIA may be at the root of AOSD development with the same instigator. In this context, we present three cases of patients diagnosed with AOSD, which possibly could be considered an association with ASIA, years after undergoing breast reconstruction with silicone breast implants. In one case, the patient solely received medical treatment due to her refusal to have the implant removed, resulting in multiple flares and severe complications related to glucocorticoid therapy. Conversely, in the other two cases, a combination of immunosuppressive therapy and silicone breast implant explantation led to the complete resolution of clinical symptoms. To the best of our knowledge, there are only 10 documented case reports of AOSD associated with silicone breast implants insertion. We believe this report serves as a complementary addition to prior research and offers further insights into the ongoing debate about whether explantation should be carried out early in the clinical course or not. *(Plast Reconstr Surg Glob Open 2024; 12:e5844; doi: 10.1097/GOX.0000000000005844; Published online 22 May 2024.)*

INTRODUCTION

Silicone has been used in a variety of medical prostheses due to its assumed biologically inert properties. However, in recent years, a gradual increase in reports suggesting a possible association with autoimmune soft tissue diseases has raised concerns about its safety.[1] Autoimmune syndrome induced by adjuvants (ASIA) is an uncommon clinical condition reported by Shoenfeld et al.[1] Although this syndrome remains a hypothesis with a poor scientific basis, numerous reports have been published on it so far, and the manifestations are postulated to be diverse. They encompass generalized symptoms such as chronic fatigue, myalgia, arthralgia, or dry mouth, induced by exogenous substances, specifically adjuvants, including vaccines, organisms, and silicone.[1,2] Meanwhile, adult onset Still disease (AOSD) is also a rare condition known for its nonspecific symptoms of spiking fever, arthritis, skin rash, lymphadenopathy, and serositis. The precise pathogenesis remains to be fully elucidated, but some case reports suggest that ASIA may underlie the development of AOSD with the same causative factor. In this report, we describe three cases of patients diagnosed with AOSD, which possibly could be considered an association with ASIA, years after undergoing breast reconstruction using silicone breast implants (SBIs). To the best of our knowledge, there are only 10 documented case reports linking AOSD with SBI insertion, and all of our cases met the criteria for both AOSD and ASIA. We believe this report serves as a complementary addition to previous research and provides additional insights into the ongoing debate about

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whether explantation should be carried out early in the clinical course or not.

CASE REPORT

Case 1

A 65-year-old woman presented to our internal medicine department due to a 1.5-week history of fever, severe fatigue, headache, and sore throat. Her medical history was unremarkable, except for right breast cancer treated with a total mastectomy and breast reconstruction using the textured type of SBIs 5 years earlier. She also developed sporadic pinkish rashes on her lower extremities accompanied by itchiness.

Laboratory tests showed a normal leukocyte count but significantly elevated C-reactive protein (CRP) at 3.74 mg/dL (reference: 0–0.3 mg/dL), ferritin levels at 14,272.9 ng/mL (reference: 12–60 ng/mL), Alanine aminotransferase (ALT) at 45 U/L (reference: 6-27 U/L), and aspartate aminotransferase (AST) at 113 U/L (reference: 13-33 U/L). The antinuclear antibody (ANA) test and rheumatoid factor (RF) test were negative. She was not taking any medication, and her family and travel history were not significant. No lymphadenopathy, arthritis, or hepatosplenomegaly was found. Computed tomography (CT) angiography was unremarkable, and there was no effusion around the SBI. Echocardiography and blood culture tests revealed no signs of infection, and further workups for specific infectious diseases, such as tuberculosis, hepatitis B virus (HBV), hepatitis C virus (HCV), syphilis, and human immunodeficiency virus, were negative.

Although these examinations could not completely rule out the possibility of malignant diseases such as lymphoma, the most likely clinical diagnosis of AOSD was made according to the Yamaguchi criteria (two major symptoms and three minor symptoms were present; Table 1).[3] Prednisone at 45 mg was initiated. Subsequent alleviation of fever was achieved, and the ferritin level showed a downward trend. However, concerns about the flare-ups remained due to mildly elevated CRP and ferritin levels. The patient expressed a preference for the removal of the SBI. Consequently, SBI explantation and capsulectomy were performed 2 weeks after the initiation of medical treatment (Fig. 1). A long-lasting total remission was confirmed after the surgical operation, and subsequent laboratory tests indicated that serum CRP and ferritin levels had returned to normal. Steroid therapy was discontinued 6 months postoperatively.

Table 1. Yamaguchi Criteria for Diagnosis of Adult-onset Still Disease

Major Criteria
• Fever of at least 39°C lasting at least 1 wk
• Arthralgia of arthritis lasting at least 2 wk
• Typical rash
• Leukocytosis > 10,000/mm with >80% polymorphonuclear cells
• Sore throat
Minor Criteria
• Lymphadenopathy
• Hepatomegaly or splenomegaly
• Abnormal liver function tests
• Negative tests for antinuclear antibody and rheumatoid factor
Exclusion Criteria
• Infections
• Malignancies
• Other rheumatoid diseases

Five or more criteria with two or more being major criteria for diagnosis of adult-onset Still disease.

Takeaways

Question: Should breast implant explantation be performed early in the clinical course or not?

Findings: One case treated without explantation ended up with multiple flares and severe complications related to glucocorticoid therapy, whereas the other two cases with explantation saw the complete resolution of clinical symptoms.

Meaning: From a therapeutic viewpoint for adult-onset Still disease associated with silicone breast implant, explantation should be performed early in the clinical course, potentially resulting in the long-term improvement in clinical courses.

Case 2

A 52-year-old woman was referred to our internal medicine department, presenting with a 1.5-week history of recurrent fever, fatigue, loss of appetite, sore throat, and arthritis in her fingers. Her medical history was notable for hyperthyroidism, atrial fibrillation, and right breast cancer treated with total mastectomy and breast reconstruction using the textured type of SBI 9 years prior. She was taking only Mercazole for her hyperthyroidism. Family and travel history were unremarkable.

Laboratory tests revealed a marked inflammatory response, including leukocytosis of 14,820 per μL (reference: 3300–8600/μL) with neutrophilia at 84.5%, a CRP

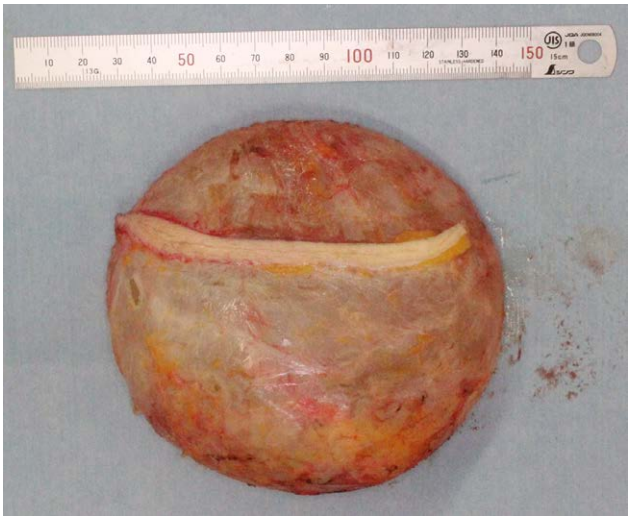

Fig. 1. The removed SBI with the capsule remaining intact and not exhibiting any visible signs of inflammation or granulation.

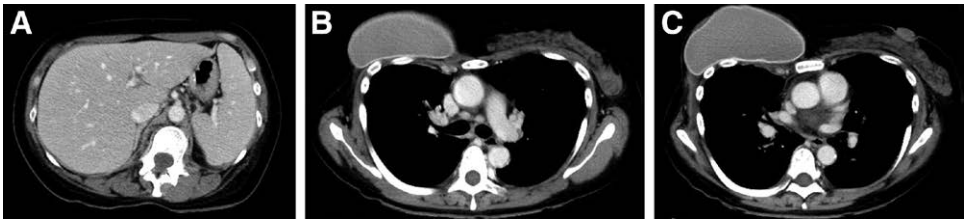

Fig. 2. CT angiography findings. A, Preoperative CT scan image revealing significant hepatosplenomegaly. B, Preoperative CT scan image showing multiple lymphadenopathy in the mediastinum and parasternal region. C, Preoperative CT scan image showing that the SBI exhibited no sign of leakage or inflammatory reaction to the surrounding tissue.

level of 9.31 (reference: 0–0.3 mg/dL), a high ferritin level of 11,506.3 ng per mL (reference: 12–60 ng/mL), ALT levels of 188 U per L (reference: 6–27 U/L), and AST levels of 124 U per L (reference: 13–33 U/L). Thyroid function tests were normal, and ANA, RF, and antineutrophil cytoplasmic antibody tests were all negative. CT angiography revealed prominent hepatosplenomegaly and mediastinal lymphadenopathy (Fig. 2A, B). There was no sign of fluid accumulation around the envelope of the SBI (Fig. 2C). Despite bone marrow aspiration, echocardiography, and further blood workups, a specific infectious agent or malignant disease could not be identified. As her symptoms met the Yamaguchi criteria (three major symptoms and all minor symptoms were present), a probable diagnosis of AOSD was made by exclusion (Table 1).[3] She began treatment with glucocorticoid therapy and prophylactic antibiotics. Although these medications provided short-lived remission, she insidiously developed drug-induced febrile neutropenia, presumably due to one of the prophylactic antibiotics. Medication adjustments for the antibiotics were made, leading to a spontaneous improvement in granulocyte count and fever.

She was subsequently referred to our department for the definitive surgical approach of SBI removal and capsulectomy. The surgical operation, performed 5 weeks after the initiation of medical treatment, significantly altered her clinical course, resulting in a complete remission of her symptoms and normalization of serum ferritin level, liver enzyme levels, and leukocytosis. Consequently, she achieved freedom from glucocorticoid therapy 7 months postoperatively.

Case 3

An 81-year-old woman developed persistent fever, polyarthritis, malaise, nocturnal sweating, and bilateral lower-extremity edema. She also noticed pruritic erythema on her anterior chest and neck. Her prior medical history included diabetes, osteoporosis, atrial fibrillation, a left femoral neck fracture, and right breast cancer treated with total mastectomy and insertion of the textured-type SBI four years earlier. Blood analysis revealed a high CRP level of 7.02 (reference: 0–0.3 mg/dL) with a normal leukocyte count, ferritin level of 2590.3 ng per mL (reference: 12–60 ng/mL), ALT level of 56 U/L (reference: 6–27 U/L), and AST level of 67 U/L (reference: 13–33 U/L). The ANA test and RF test were negative. CT angiography showed that the SBI remained intact, but there was hepatosplenomegaly and mediastinal lymphadenopathy. Further comprehensive workups could not provide any evidence suggesting an infectious or malignant etiology.

According to the Yamaguchi criteria (two major symptoms and four minor symptoms were present), she was deemed to be experiencing AOSD, and prednisone therapy at 1 mg per kg was started (Table 1).[3] Although she obtained temporary improvement in her symptoms and laboratory abnormalities, she shortly had flare-ups, requiring higher steroid doses and the addition of immunosuppressive therapy. The removal of the SBI had been repeatedly recommended to the patient, but she kept declining. Any other potent medical therapy could not succeed in stabilizing her condition.

Almost half a year after her initial visit to our hospital, she developed a severe soft tissue infection with worsening swelling and ulceration in her lower extremities, which eventually led to pseudomonas septicemia and, tragically, resulted in her death several months later.

DISCUSSION

Given some evidence of a possible causal link between SBIs and autoimmune connective-tissue diseases, further continuous study on whether silicone is always biologically inert or not appears to be necessary. Several reports have suggested a significantly higher incidence of systemic symptoms, such as arthralgia, malaise, or myalgia, in women with breast implants.[4,5] These autoinflammatory responses, mainly characterized by musculoskeletal pain or severe fatigue, have been described as siliconosis. The causational link remains controversial, with some meta-analyses suggesting no causal association between breast implants and connective-tissue diseases.[2,6,7] However, most of the symptoms in patients with breast implants are frequently too nonspecific or indistinct to classify into any specific diseases, making it challenging to explore the causal relationship.[8] Shoenfeld et al[1] hypothesized a more comprehensive medical condition called ASIA, where certain adjuvants like silicone trigger immunological dysregulation, leading to a wide range of systemic autoimmune symptoms, especially in genetically predisposed patients. While this syndrome has not been supported by a definitive epidemiological or etiological study, numerous reports on it have been published so far. This does not necessarily validate the clinical condition scientifically, but it does imply that many clinicians have encountered

similar, confusing circumstances evoking this condition. It might be valuable for practitioners involved in breast reconstruction to keep this clinical concept in mind during clinical follow-ups.

To the best of our knowledge, there are only 10 case reports of AOSD, which is reportedly associated with ASIA following SBI insertion.[9–12] This condition is assumed to be a rare subtype of ASIA, and the ideal therapeutic strategy has yet to be standardized.[11] Medical treatment mainly follows the therapeutic strategy for conventional AOSD. It is widely accepted to use glucocorticoids as a major part of the treatment and to consider the addition of methotrexate or biological agents like tocilizumab or infliximab, depending on the clinical course.[11] There remains controversy regarding whether explantation should be performed. In this report, two of three cases were treated with concurrent surgical removal of SBIs, and the surgical operations significantly contributed to the improvement of patients' symptoms, abnormal inflammatory blood parameters, and the reduction in the amount of steroids. On the other hand, one case was treated solely with long-term glucocorticoid therapy and immunosuppressive therapy without SBI explantation, failing to achieve a stable medical condition, eventually leading to severe sepsis due to the side effects of medical therapy. This cautionary case underscores the significance of SBI removal in reducing the risk of complications associated with prolonged use of steroids or immunosuppressive agents and stabilizing the medical condition. Although medical treatment has been the first choice for AOSD associated with SBIs implantation, the implementation of SBI explantation should be reflected on early in the therapeutic course, especially when symptom flare-ups occur even once after the initiation of medical therapy or in patients with a significant medical history or family history of autoimmune diseases.

There are some limitations in this report. It is certainly possible that these patients might have had different factors contributing to the development of AOSD or that their symptoms might have improved spontaneously. However, we observed a significant improvement in the patients' symptoms and laboratory findings just after the SBI removal in case 1 and 2. We believe that the clinical course notably supports the coherence of our discussion.

It is noteworthy that no rupture was found in any of the SBIs in these reported cases, and the pathological analysis of the removed capsules revealed no infiltration of inflammatory cells or silicone bodies. Silicone might begin to leach into these capsules considerably over the years ahead, as reported by McConnell et al, who found a significant correlation between silicone concentration in capsular tissue surrounding intact implants and the duration of implantation.[13] Our findings suggest that the infiltration of silicone body into the capsular tissue or direct exposure to silicone gel is not necessary for the development of autoimmune reactions. There is a possibility that the clinical condition might be instigated merely through contact with the envelope of SBIs, which is also chiefly composed of silicone; whether SBIs have any damage or leakage has little bearing on the indication for surgical treatment.

In this report, we presented three cases of AOSD, which could possibly be considered an association with ASIA, after breast reconstruction with SBIs. Although it is a rare clinical condition without a standardized optimal treatment strategy, proactive stance on the surgical approach, regardless of whether SBIs have defects, can potentially result in the long-term improvement in clinical courses.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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All procedures conformed to the principles set forth in the Declaration of Helsinki. This study was approved by the ethics committee of Sakai City Medical Center, and informed written consent to publish personal and medical information was obtained from the patients.

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