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Autoimmune / Inflammatory Syndrome Induced by Adjuvants (Asia Syndrome) Associated with Silicone Breast Implant Rupture

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ABSTRACT

Background: Autoimmune/inflammatory syndrome (ASIA) constitutes a set of related immune mediated diseases that share a common clinical picture and a history of a previous exposure to an adjuvant agent. From a clinical standpoint, patients present with none specific manifestations such as myalgia, arthralgia, chronic fatigue and dry mouth as well as neurological manifestations such as cognitive disturbances, memory loss and neurologic disabilities.

Case presentation: A previously healthy 25-year-old patient who underwent breast augmentation 3 years ago, with an asymptomatic rupture of the silicone breast implant, presented with three major criteria of ASIA, and improved after bilateral implant removal. She also had pleuritis and pericarditis, rarely described in such disease. A literature review on complications related to breast implants, their questionable relationship to the onset of autoimmune pathologies, and basic aspects of the diagnosis and management of ASIA was carried out.

Conclusion: The silicone presented in breast implants should be considered as an adjuvant, with the potential to cause chronic stimulation to the immune system. This can lead to systemic manifestations that can be severe in patients genetically predisposed and potentially not reversible even after surgical removal of the implants. When facing patients with breast implants and systemic clinical symptoms, lymph node disorders, neurological manifestations, or serositis as in the case presented, without other defined etiology, the possibility of ASIA should be considered in the differential diagnosis.

Introduction

Silicone breast implants have been used for reconstructions and cosmetic purposes since 1960.[1] Breast augmentation mammoplasty using silicone implants is the most commonly performed cosmetic surgery in the United States, with approximately 300,000 procedures performed per year.[2] This is also observed in Brazil, according to the biannual consensus of the Brazilian Society of Plastic Surgery of 2018.[3] The initial generations of breast implants had high rupture rates and the suspicion of their relationship with collagen diseases caused the US Food and Drug Administration to suspend its use in 1992. This decision was revoked in 2006, after improvements made by manufacturers and the absence of conclusive evidence of the association between implants and collagen diseases.[4-6] However, the association of silicone implants with systemic pathologies, such as lymphoma, ASIA and other autoimmune diseases, has been questioned in some studies.[7]

Autoimmune/Inflammatory syndrome, induced by adjuvants (ASIA), is a disease that was first introduced by Shoenfeld et al. in 2011.[8] It constitutes

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Table 1. Suggested criteria for ASIA diagnosis

MAJOR CRITERIA
1. Exposure to external stimuli (infection, vaccine, silicone, other adjuvants), before the onset of symptoms.
2. Presentation of at least one of the following symptoms:
- Muscle weakness, myalgia, or myositis;
- Arthritis or arthralgia;
- Chronic fatigue, poor restorative sleep, or other sleep disorders;
- Neurological manifestations (especially those associated with demyelination);
- Cognitive or memory deficit;
- Fever, dry mouth.
3. Improvement of symptoms after removal of the adjuvant.
4. Typical biopsy of the organs involved.
MINOR CRITERIA
- Presence of autoantibodies or antibodies directed to the adjuvant.
- Other clinical manifestations (e.g., irritable bowel syndrome)
- Specific HLA (e.g., HLA, DRB1, HLA DQB1)
- Presentation of an autoimmune disease (e.g., multiple sclerosis, systemic sclerosis)

a set of closely related immune mediated diseases that share a common clinical picture as well as a history of previous exposure to an adjuvant agent, silicone being one of them.[9] Shoenfeld et al. have proposed several major and minor criteria that may aid in the diagnosis of ASIA syndrome (Table 1).

The diagnosis of the disease is made by the presence of at least 2 major criteria or 1 major criterion and two minor ones.[8]

From 2011 until 2016, more than 4000 documented cases of ASIA syndrome were reported with various clinical severity and diverse history of adjuvant exposure.[10] There is little known about geographical distribution[11], although many of the autoimmune diseases are more prevalent in populations that live further away from the equator as it is believed that limited exposure to sun, and therefore the lack of production of vitamin D, may be associated with ASIA.[12] In this report, we present the case of a 25-year-old patient who underwent breast augmentation 3 years ago, with an asymptomatic rupture of the silicone breast implant, who presented three of the major criteria for ASIA (exposure to external stimulus (silicone), symptoms of fever and fatigue and complete improvement after removal of the adjuvant).

A literature review was conducted using PubMed, MEDLINE and Cochrane databases by searching for the keywords. Subsequently, additional papers were located by bibliography review and through manual searching until February 2021 when the review ended. Papers were included if they specifically discussed ASIA in the setting of silicone breast implants, Shoenfeld's syndrome, Breast prosthesis syndrome, Silicone and implant incompatibility syndrome (SIIS). Only articles written in English in the adult population were included. The relevant literature was then analyzed to determine whether consensus existed on the topics discussed in the present case.

We consider it worthwhile to highlight that there is a certain heterogeneity in the terminology used for autoimmune/inflammatory reactions related to silicone implants. While "siliconosis" is one of the diseases included in ASIA by Schoenfeld et al.[13], the term "Silicone implant incompatibility syndrome (SIIS) is defined as having symptoms or signs of silicone allergy, capsular contracture, and/or systemic manifestations such as chronic fatigue, arthralgia, myalgias, asthenia, and/or fever, which do not fulfilled Shoenfeld's criteria for ASIA.[13] Also, "Breast prosthesis syndrome" is defined as a specific immune disease related to breast implants, a mixed autoimmune disease or non-specific immunological disease, characterized by clinical findings very similar to ASIA, such as arthralgia, chronic fatigue, myalgia, fever, sleep disturbances, among others, but without well-defined diagnostic criteria.[14]

Case Presentation

A previously healthy 25-year-old patient who underwent breast augmentation with the placement of silicone implants in November 2018, sought hospital care 11 months after the surgical procedure, complaining of persistent fever, severe chest pain, which used to get worse at bedtime, besides dyspnea, general malaise, and fatigue for 15 days. Physical examination revealed painful axillary and infraclavicular lymph node enlargements on the left.

Initial blood work showed an increase in CRP (167mg / dL) and the WBC count was normal (4.900/mm3). In the posterior investigation for rheumatological conditions, the tests for Antinuclear Antibodies (ANA), the erythrocyte sedimentation rate and rheumatoid factor were negative. The hepatitis and HIV serology were also negative. Echocardiogram showed slightly increased refringence of the posterior pericardium, with a small associated pericardial effusion, without segmental changes in contractility. Chest tomography in addition to pericardial effusion (Figure 1) showed axillary, infraclavicular, and parasternal lymph nodes on the left, some with a necrotic center, associated with inflammatory changes in the adjacent soft tissues (Figure 2). Despite the

limitation of the tomography in viewing the breast implants, due to the irregularity of their contours on the left, the hypothesis of rupture of the breast implant on this side was suspected (Figure 3).

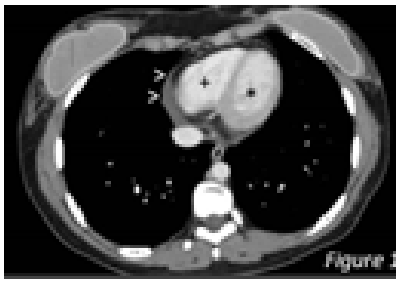

Figure 1. CT image of the chest after injection of the contrast medium, at the level of the right (*) and left (+) ventricles, showing a hypodense image, with a lentiform aspect, in the topography of the pericardium, compatible with a small pericardial effusion (>).

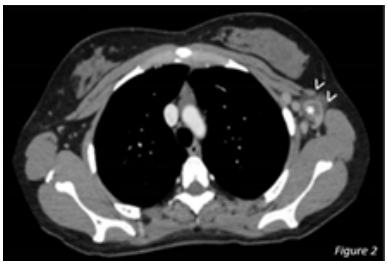

Figure 2. CT image of the chest after injection of the contrast medium, showing axillary lymph nodes enlargement (<), one of them with a hypodense and hypocaptant center, suggestive of necrosis (*).

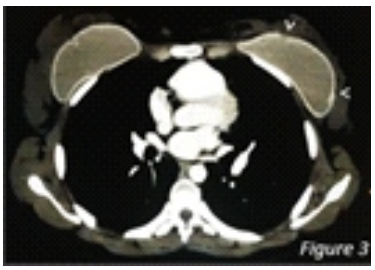

Figure 3. CT image of the chest, after injection of the contrast medium, showing irregularities in the contours of the capsule of the left breast implant (<).

Breast ultrasonography showed regularities in left implant contours and collection surrounding it, suggestive of intracapsular rupture (Figure 4). Axillary, infraclavicular, and parasternal lymph nodes were also observed on the left, with a “snow storm” shadow (Figure 5), indicating extracapsular silicone.

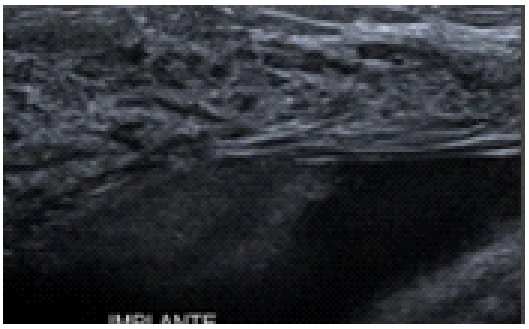

Figure 4. US image of the left breast, showing poorly defined collection of the implant, an indirect sign of rupture.

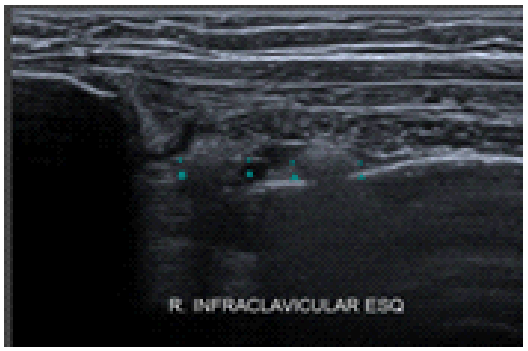

Figure 5. US images of the infraclavicular region, showing lymph nodes with "snowstorm" shadow (+), indicative of silicone-associated lymph node disease.

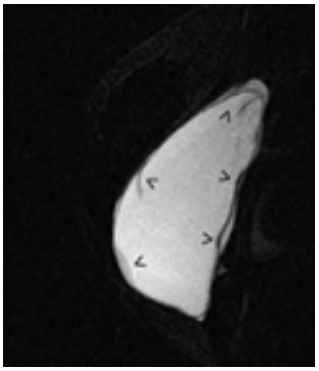

Figure 6. MRI image of the left breast, weighted in sequence for silicone, showing curvilinear hypo signal lines inside the implant (>), characterizing the linguini sign, suggestive of intracapsular rupture.

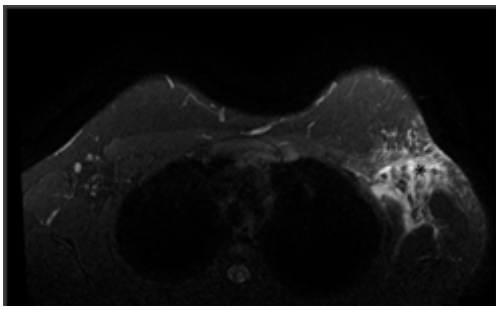

Figure 7. MRI image of the breasts and armpits, weighted in T2WI with fat suppression, showing an extensive inflammatory process in the left axilla, characterized by heterogeneous hypersignal (*) in this topography.

MRI of the breasts was performed, which showed an intracapsular rupture of the left breast implant (Figure 6) and axillary lymphadenopathies on this side with adjacent edema (Figure 7).

The patient underwent an excisional biopsy of the largest left axillary lymph node, which demonstrated necrotizing lymphadenitis associated with foreign body material, compatible with extracapsular silicone. Bilateral surgical extraction of the breast implants was performed, thirty-five days after the beginning of the symptoms, followed by cleaning of the surgical stores and biopsy of the implant capsules. During the surgical procedure, it was observed that the right implant was intact, but with non-compliant liquid, compatible with silicone. While the left implant had an intracapsular rupture, with a large amount of intracapsular silicone around the implant and a fibrotic capsule. Complete resolution of symptoms was reported in clinical control one month after the surgical procedure. The patient was symptom-free 16 months after surgery.

Pathologic examination of the capsule of the right implant showed synovial metaplasia, characterized by fibrohistiocytic cells covering one of the faces, polarized perpendicularly to the surface. The biopsy of the left capsule also showed synovial metaplasia, in addition to several foci of foreign body reaction to silicone-compatible material. Immunohistochemistry (IHC) was not done.

Three major criteria for ASIA were fulfilled, including exposure to external stimulus (silicone), symptoms of fever and fatigue, in addition to symptoms improvement after removal of the adjuvant, and no identification of other causal factors for the symptoms, even after investigation.

Discussion

Silicone breast implants have been used for reconstructions and cosmetic purposes since 1960.[1] They are composed of a silicone elastomer envelope and filled with gel-shaped silicone.[15] Although silicone does not have a direct effect on the immune system, it has been suggested that it may have an effect as an adjuvant. The agent whose function is to direct the immune system to the production of antibodies (humoral response) or to the stimulation of T lymphocytes (cell-mediated reaction) is called adjuvant, in order to intensify the immune reaction. Thus, even if the immune system does not react specifically to silicone, this substance can favor an immune reaction to other antigens, triggering autoimmune, and connective tissue diseases, in genetically predisposed patients.[16] The initial generations of breast implants had high rupture rates and the suspicion of their relationship with collagen diseases caused the US Food and Drug Administration to suspend its use in 1992. This decision was revoked in 2006, after improvements made by manufacturers and the absence of conclusive evidence of the association between implants and collagen diseases.[4-6]

There are still controversies today about the possibility of silicone implants being related to autoimmunity reactions.[17] Decades after the description of the first case of the syndrome described as "Breast disease by adjuvant"[18], a pathology that did not fit into the typical connective tissue disease and that was called adjuvant-induced autoimmune syndrome (ASIA) was recognized, related to silicone[13]. Resembling other autoimmune disease entities, the etiopathogenesis of these conditions involves a multifactorial interplay between environmental factors and genetic predisposition as noted by the association with certain HLA haplotypes.[11] In part, the mechanism involves the chronic stimulation of the immune system, which may then lead to the release of inflammatory cytokines including interferon γ, interferon α, interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)α and so forth. Therefore, this syndrome can, in part, be induced by this cascade of cytokines released in response to the chronic stimulation.[11]

Patients who develop ASIA may present a series of specific and non-specific manifestations, with very heterogeneous clinical manifestations, which can be more severe in patients with breast implant rupture. The interval between implantation/rupture and the presentation of symptoms is quite variable. The diagnosis of the disease is made by the presence of at least 2 major criteria or 1 major criterion and two minor ones, detailed in Table 1.[8]

In the case presented in this report, the patient presented a silent intracapsular unilateral silicone breast implant rupture. Intracapsular rupture of implants is the most common type, accounting for 77-89% of all ruptures.[19] Extracapsular rupture, on the other hand, is less frequent and is characterized by the leakage of silicone through the fibrous capsule, involving the adjacent mammary parenchyma.[20] Ultrasonography detects ruptures in silicone implants with a sensitivity of about 50-77% and specificity between 55 and 84%. The most specific ultrasound signal is the visualization of multiple elongated, hyperechogenic, linear, or curvilinear images, inside the implant, called the stair sign.[21] Magnetic resonance imaging has high sensitivity and specificity for detecting implant ruptures, approximately 72-94% and 85-100%, respectively.[22] The most specific finding of intracapsular rupture is called the "linguine sign", which is characterized by layers of the silicone elastomer capsule, collapsed inside the silicone gel, contained by the fibrous capsule.[23]

Caravantes et al.[14] published a review in which they recommend performing, as part of the pre-operative evaluation, the determination of family and pathological clinical history, immunological markers (antithyroid antibodies, rheumatoid factor, ESR, immunoglobulins, antinuclear antibodies and C-reactive protein) and mammography or ultrasound, depending on whether the patient's age is greater than or less than 40 years. In the case of patients without any risk factor, the follow-up after silicone breast implant placement consists of

assessment every two years for ten years with ultrasound and immunological markers. In the case of positive history or immunological markers, rheumatology assessment is confirmed and the follow-up consists of ultrasound once a year, MRI after 5 and 10 years and immunological markers in the first year and every two years for 10 years.

Fuzzard et al.[24] published a literature review where they suggest an algorithm that begins with a clear informed consent process and identification of risk factors for SIIS development prior to implantation. Subsequently, if SIIS develops, they advocate early multidisciplinary input. The first line treatment strategy should be centered around patient education and acknowledgement of their symptoms. If this fails to alleviate the condition, medical management should be trialed under the guidance of an autoimmune specialist. In the cohort of patients who have additional ongoing issues, explantation is recommended.

Mizuno, Y. et al.[25] conclude that when patients with silicone breast implants present with pleuritis or pericarditis, physicians should consider the possibility of implant rupture and explanation. Shaik IH et al.[26] presented a case of recurrent pleural effusion related to breast implants where dramatic improvement of pain and effusion after removal of implants was helpful in confirming the diagnosis and treatment. Dagan A. et al.[27], described a case of adult-onset Still's disease (AOSD) associated with breast augmentation as part of autoimmune syndrome induced by adjuvants (ASIA), manifested with pleuritis and pericarditis, developed after breast mammoplasty, concluding that, since some patients do recover from the AOSD with medical treatment only, this should be the first line of action. If the patient fails to recover with medical treatment, as was in the present case, an imaging study, preferably MRI of the breasts, should be done to detect leakage- and surgery should be discussed with the patient.

In conclusion, the silicone present in breast implants should be considered as an adjuvant, with the potential to cause chronic stimulation to the immune system. This can lead to systemic manifestations that can be severe in genetically predisposed patients and is potentially not reversible even after surgical removal of the implants. Among patients with breast implants and systemic clinical symptoms, lymph node disorders, neurological manifestations, or serositis as in the case presented, without other defined etiology, the possibility of ASIA should be considered in the diagnosis.

Conflicts of Interest

The authors declare that they have no conflict of interest related to the publication of this manuscript.

Ethical Consideration

The description and publication of the case was authorized by the patient through informed consent.

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