International Journal of Research in Medical Sciences
Gardea VMB et al. Int J Res Med Sci. 2023 Aug;11(8):3105-3109
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20232458

Review Article

Autoimmune/inflammatory syndrome induced by adjuvants: a review

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Received: 08 July 2023
Accepted: 21 July 2023

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ABSTRACT

The autoimmune/inflammatory syndrome induced by adjuvants (ASIA) includes several autoimmune conditions and phenomena that occur after exposure to substances with adjuvant activity. The spectrum of the disease is heterogeneous with respect to the clinical presentation as well as the severity of the clinical manifestations. Different substances and medical devices with adjuvant activity are currently known, such as vaccines, oils, silicones, mineral salts, lipopolysaccharides, peptidoglycans, among others. These adjuvants are immunological molecules that function through potentiation of antigen-specific immune responses. Thus, the etiopathogenesis of ASIA syndrome involves a multifactorial interaction between environmental factors and genetic predisposition, and secondary activation of the adaptive and innate arms of the immune system through various mechanisms. Although in some reported cases the ASIA syndrome improves considerably when removing the implants, there are no conclusive results for the clinical benefit of removing the implants, so it is necessary to carry out further basic, clinical and surgical investigations in order to determine the best therapeutic decision.

Keywords: Autoimmune/inflammatory syndrome induced by adjuvants, Medical devices, Autoimmunity, Breast implants, Silicone breast implantation

INTRODUCTION

The autoimmune/inflammatory syndrome induced by adjuvants (ASIA) syndrome includes various conditions and/or autoimmune phenomena that are induced after exposure to substances with adjuvant activity. Among the group of substances most commonly used are silicones that are used for various medical-surgical applications for aesthetic purposes, such as implants. mammary and rhinoplasty as well as the recent so-called facial harmonizations in which different health personnel are involved in Mexico from dentists, aesthetic doctors, to medical subspecialties and non-aesthetic doctors. Its use also covers non-aesthetic applications such as hydrocephalus shunts, catheter lines, intraocular implants, functional rhinoplasty, joint implants, among others.[1] When silicones were introduced medically in the 1960s, they were initially thought to be biologically inert, however, in the last 50 years, it has become apparent that they may be associated with the induction of various

immunological disorders.[2] As of 2021, more than one million breast augmentation procedures have been performed worldwide – although many consequences ensued and are becoming increasingly reported. A large number of these events have been reported to the FDA with an increasing number of women requesting surgical removal of the breast implants based on these adverse events: local complications such as chronic pain; migration of the implant component towards the lung, skin or extremities; capsular rupture and contraction; allergy; and ASIA syndrome, systemic inflammatory symptoms such as those present in autoimmune rheumatic diseases and the development of lymphomas.[2]

In 2011, a syndrome entitled ASIA (Shoenfeld's syndrome) was first described.[3] Adjuvants are compounds that, when interacting with the organism, can improve an immunological reaction with the subsequent elevation of antibodies.[4] Genetic predisposition plays an important role, it occurs more frequently in people who carry genes such as HLA DQ2 and DRW53.

Some examples of builders are aluminum hydroxide, squalene, and silica.[5] Recent studies have shown that human medical implants, including injectable ones such as silicones and polypropylene meshes, can act as adjuvants.[6]

ASIA DUE TO MEDICAL IMPLANTS

The possible development of ASIA syndrome has been considered in patients who have undergone mammary or testicular implants, rhinoplasty, repair of different hernias with the use of polypropylene mesh, as well as prosthetic materials for arthroplasty and/or metallic implants in orthopedics.[7]

Patients with an allergic past medical history are at a greater risk of developing ASIA after implantation. Furthermore, patients with an established autoimmune disease or a familial predisposition to autoimmune disease are at risk of developing symptoms after silicone breast implantation ("SBI"). It is important to note the interplay between immunogenetic (i.e., human leukocyte antigens "HLA") factors as well as environmental factors such as smoking and obesity in the development of medical device induced ASIA.[8]

PATHOPHYSIOLOGY

In general, commonly used biomaterials for implantation are nonimmunogenic and non-toxic. However, implanted biomaterials trigger a foreign body reaction (FBR) resulting in granulomatous inflammation.[9]

Immediately after the initial interaction between the biomaterial-organism, a phagocytic reaction (predominantly macrophages of the pro-inflammatory subtype M1) induced by protein uptake occurs, as well as the presence of activated mast cells and histamine which in this context plays a fundamental role in pain that can be moderate-intense at the implantation site secondary to sensitization of the transient reporter potential channel V1 (TRPV1), a nociceptor.[10-12]

The chronic inflammatory response is related to peri-implant microbial biofilms; biomaterials act as an adjuvant in the development of an adaptive immune response to an antigen.[6] With the recent investigations carried out, it has been possible to demonstrate that the inflammatory response in these situations is due to a multiple and complex interaction between proinflammatory factors, cytokines, cellular elements and cellular signaling pathways.[13]

Silicone implants have generally been associated with acute inflammatory processes, which can evolve into chronic inflammatory processes, with which there is the consequent risk of developing a granulomatous disease, favoring the formation of capsules and fibrosis.[14,15] Some authors report that the inflammatory triggering process is secondary to subclinical bacterial infection.[16]

Staphylococcus epidermis, as part of the resident mammary flora, causes the formation of a biofilm when it comes into contact with the surface of the silicone and produces a periprosthetic inflammation that stimulates the formation of IL-6, which inhibits the generation of regulatory T cells. This determines that, in long-term stimulation, there is a more significant effect of the effector T cells and consequently, a more significant response of activated TH1/TH17 cells. the activation of the immune system suppresses the regulatory T cells that, together with IL-17, carry out the stimulation of those responsible for the immune response such as Th1/Th17, IL-17, IL-6, IL-8, transforming growth factor (TGF)-b1, interferon (IFN); stimulating and maintaining the active inflammatory and immune response, as occurs in late stages of chronic inflammatory responses.[17]

DIAGNOSIS

Typical clinical symptoms of ASIA are: chronic fatigue, arthralgias, myalgias, pyrexia, sicca symptoms, cognitive impairment, and or (atypical) neurological symptoms, nonrestorative sleep.[2] Patients often suffer from severe morning stiffness, myalgias and/or muscle weakness. Weakness can be severe and may render the patient bedridden.

Furthermore, most patients report pyrexia and night sweats, while others report dry eyes and/ or a dry mouth. Dry eyes are often severe and may result in blurred vision and/or a keratitis sicca if left untreated.[8] The diagnosis of this disease is complicated and most of the time it is reached by exclusion, since there are no specific diagnostic tests, so it is necessary to carry out a complete clinical history, history and a detailed physical examination. The clinical picture is highly variable, with different

symptoms, among which we can demonstrate arthralgia, muscle weakness, chronic fatigue, cognitive and memory impairment, sleep disorders, pain, among others.

Shoenfeld and Agmon-Levin propose a table with major and minor criteria with which they have been modified over time, with which a more precise diagnosis of ASIA syndrome can be made.[3,18]

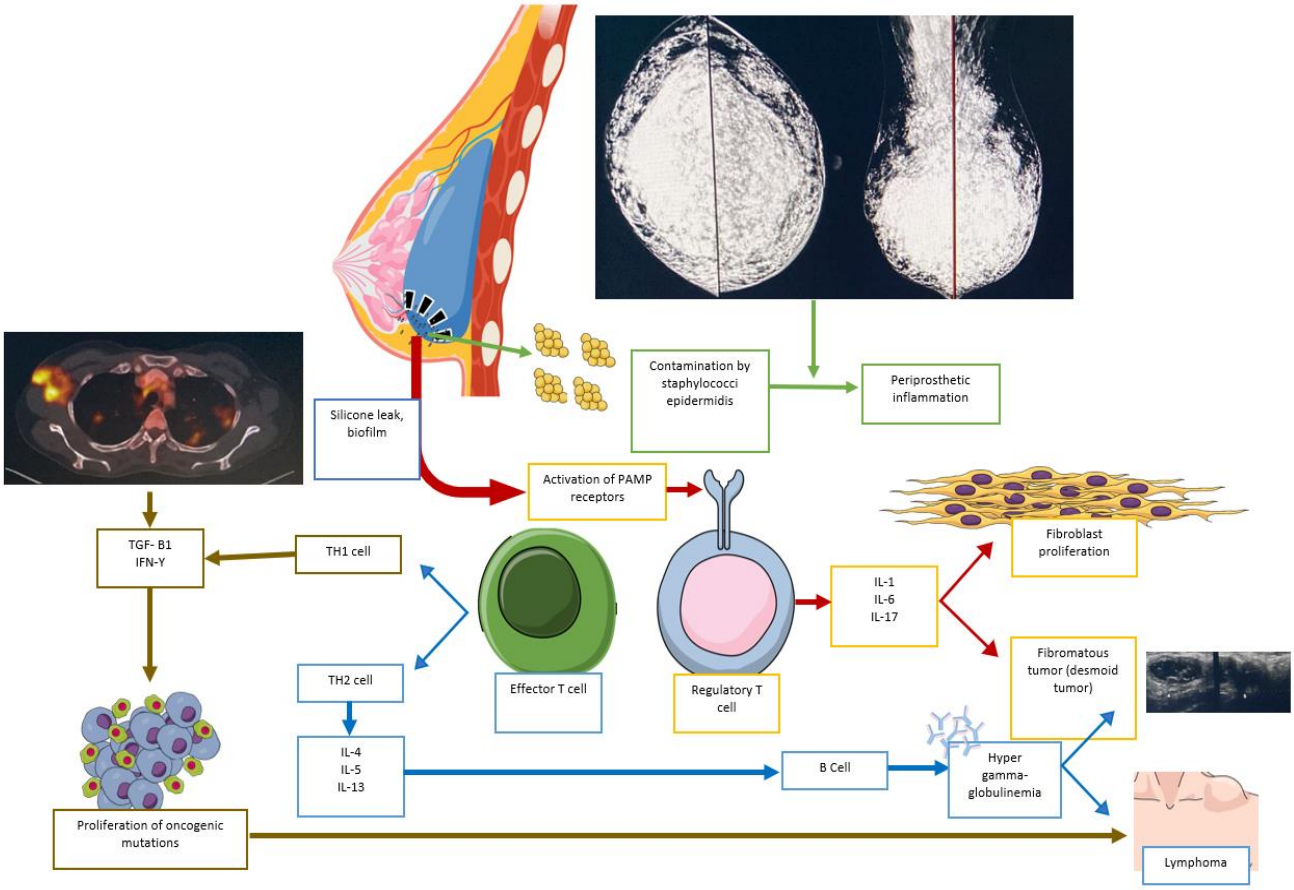

Figure 1: ASIA syndrome pathophysiology- summary description of the possible pathophysiological pathways in the development of ASIA syndrome, as well as inflammatory and autoimmune processes.

Figure 2: Magnetic resonance in relation to minimally collapsed intracapsular rupture of the right mammary implant (A) lobed edges of the right mammary prosthesis with a maximum capsule thickness of 0.3 cm, linguini sign and radial folds are identified, scant periprosthetic fluid is observed, predominantly hypodense on the left on T1 sequences; (B and C) carce hyperdense periprosthetic fluid on T2 and STIR.

Note-*scattered bilateral fibroglandular breast tissue with bilateral retroalleoral predominance, without evidence of glandular lesions.

More than a decade after the first description of the ASIA syndrome, new cases and the list of potential adjuvant materials continue to be added, especially in the area of aesthetics where it is used most frequently and in some with indiscriminate use, especially hyaluronic acid, methacrylate, polyacrylamide, polyalkylimide and metals in implants as used in orthopedic surgery and/or in contraceptive devices.[7,19]

Although hyaluronic acid filler is the only substance approved by the U. S. Food and Drug Administration (FDA), the use of analogous substances in non-FDA-approved fillers has become popular worldwide and is having an impact on the health of those on whom they are used. In general, the materials used include substances such as industrial oils, silicone, methacrylate, collagen, paraffin, among others. The use of these substances, in the short or long term, causes various manifestations and complications for those who receive them. Some authors think that these problems have reached epidemic proportions, especially in Latin America.[20,21]

CONCLUSION

Although in some reported cases the ASIA syndrome improves considerably when removing the implants, there are no conclusive results for the clinical benefit of removing the implants, so it is necessary to carry out further basic, clinical and surgical investigations in order to determine the best therapeutic decision.

ACKNOWLEDGEMENTS

Authors are thankful to Dr. Graniel-Palafox L. and Dr. Argüelles-Castillo C. N. for the imaging studies.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Gardea VMB, Ramos JHB, Trejo OAA, Rodríguez AGD, Acosta JRM, Salcido MB, et al. Autoimmune/inflammatory syndrome induced by adjuvants: a review. Int J Res Med Sci 2023;11:3105-9.