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# Autoimmune Syndrome Induced by Adjuvants and Breast Implant Associated Anaplastic Large Cell Lymphoma: An Analysis

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**ABSTRACT**

The Adjuvant-Induced Autoimmune/Inflammatory Syndrome is caused by humoral mediators that lead to capsular contracture and fibrosis by the oxidation that occurs in the silicone. Anaplastic Large Cell Lymphoma occurs through the development of a seroma, with the formation of periprosthetic effusion or by an infiltration of the pathology itself, causing a tumoral growth inside and outside the capsule. The development of lymphoma occurs through the formation of a subclinical biofilm, capsular contracture, recurrent trauma, genetic predisposition or autoimmune etiology. To analyze these affections, a literature review was carried out on the symptomatology and pathophysiology of the Adjuvant-Induced Autoimmune/Inflammatory Syndrome and Anaplastic Large Cell Lymphoma, which was searched using the terms "ASIA breast silicone" "Lymphoma" "Adjuvants" "Immunologic" "Breast Implants" in the platform PubMed. Analyzing the data obtained, it was noted that the symptoms of Adjuvant-Induced Autoimmune/Inflammatory Syndrome are nonspecific, such as fatigue, neurasthenia, myalgia, arthralgia, morning stiffness and night sweats, and, therefore, need attention. On the other hand, Anaplastic Large Cell Lymphoma presents with breast pain, periprosthetic effusion, palpable mass, among others. In view of these aspects, it is concluded that a good investigation must be carried out when nonspecific symptoms appear, regardless of the time the surgery was performed, since these complications can appear years after the surgery.

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## Introduction

The syndrome entitled ASIA - Autoimmune/inflammatory syndrome induced by adjuvants (or simply "Schoenfeld syndrome")- manifests itself as an immunological reaction provoked by triggering compounds. Among the etiologies linked to this syndrome, the exposure of the body to silicone components stands out, due to its wide use in breast implants [1].

Silicone is made up of polymeric silica, which will be the adjuvants that activate the immune and inflammatory system. From the capture of these particles by macrophages, the release of interleukins 1b (IL-1B), B cells, Th17 cells and subsequently a clonal expansion of T lymphocytes is induced. Thus, the presence of silicone may lead to the formation of autoantibodies, polyclonal hypergammaglobulinemia and even progression to lymphoma [2,3].

ASIA presents with varied systemic symptoms such as chronic fatigue, dyspnea, arthralgia, myalgia and dysphagia. However, it is important to highlight that the syndrome also predisposes patients to developing other autoimmune diseases, including rheumatic diseases, hypo- or hyperthyroidism, rheumatoid arthritis, Sjogren's syndrome, fibromyalgia and systemic lupus erythematosus [4,5].

Another consequence of breast implants is its association with Anaplastic Large Cell Lymphoma (BIA-ALCL). The development of BIA ALCL appears to be associated with three factors: the type of breast implant, genetic predisposition and biofilm formation (contamination) [1,6].

Today there are two theories that explain the pathology of BIA-ALCL: the first is the development of a seroma, with the formation of a periprosthetic effusion around the breast prosthesis or even inside the implant; the second due to the infiltrative development of the disease itself, with tumor growth inside or outside the capsule [7].

The first theory was identified as being the most common, according to Groth et al., which will have a late clinical presentation and may manifest itself as a palpable mass to lymph node involvement. It is also estimated that ALCL symptoms appear on average 9 years after implantation, enough time to screen for the disease [7].

In addition to the inflammation generated by the compound, the patient may experience "silicone leakage" - generally due to the natural wear and tear of the prosthesis - caused by the movement of low molecular weight compounds through the implant's elastomer envelope [8].

**Table 1:** Main disorders found in the literature review. *ASIA (Adjuvant-Induced Autoimmune Syndrome) BIA-ALCL (Anaplastic Large Cell Lymphoma Associated with Breast Implants)

| ASIA | BIA-ALCL |
|---|---|
| Chronic fatigue | Breast pain |
| Arthralgia | Palpable mass |
| Myalgia | Late stroke |
| Dyspnea | Periprosthetic effusion |
| Dysphagia | Breast asymmetry |
| Sjogren's syndrome | Lymph node involvement |
| Fibromyalgia | |
| Systemic lupus erythematosus | |

## Goal

The article aims to collect data on symptoms, prevalence and pathophysiology of the main complications related to silicone implants, such as ASIA and BIA-ALCL.

## Method

This research was carried out addressing the current factors that most contribute to the development of ASIA and BIA-ALCL in women, both in Brazil and in other countries. In order to guarantee the reproducibility of the information analyzed, 5 selection stages were established. Diagrammed in the flowchart below

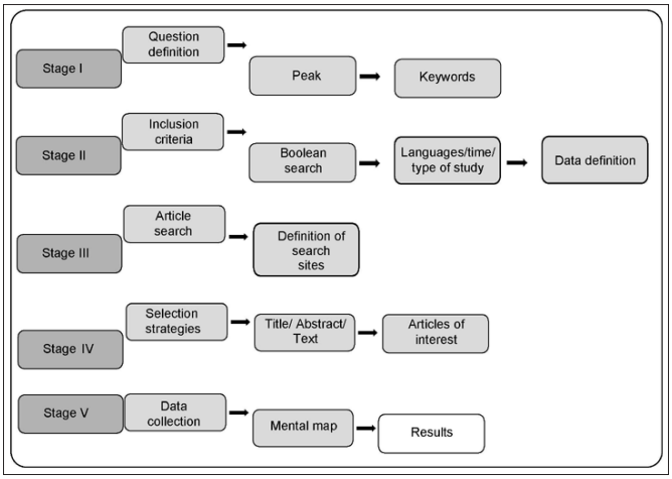


**Figure 1:** Methodology Used and Its 5 Steps

Stage I defined the research question in question: "what are the complications caused after the insertion of a silicone implant?", obtained via the PICO method.

Stage II consisted of defining the Boolean scheme that met the resolution of the research problem, as well as definitions of article eligibility, such as: [I] Having a maximum of 11 years of publication; [II]No conflicts of interest; [III] Direct relationship with the object of study and its guiding question; [IV]Availability in Portuguese, English, French and Spanish. It was also established that the initial Boolean search criteria would be based on the terms: "ASIA breast silicone", "Breast implant" "anaplastic large cell lymphoma" "silicone disease", "breast implant associated with anaplastic large cell lymphoma", "silicone implant complications".

Stage III aimed to define the article search portals, with the database being the websites of Pubmed, Science Direct and Capes Periodicals.

Stage IV constituted the selection phase of the articles found, in which the title, summary and, in cases of doubt or interest, the complete reading of the periodical were read, taking into account the answer to the research problem.

Finally, in stage V the results were analyzed, via mind maps and other instruments, with the aim of generating the results and discussions present.

## Results

In the end, a total of 968 articles were analyzed, of which 20 met the aforementioned criteria, with the aim of addressing ASIA and BIA -ALCL as possible complications of breast implants.

## Discussion

ASIA is a disease characterized by chronic pain, joint manifestations, among other symptoms. Currently, it is increasingly in the spotlight due to its correlation with silicone implants, which are increasingly widespread in society and are in high demand among young and adult women in search of a more beautiful and standardized body.

Since the 90s, prostheses have been the subject of discussion, especially due to the emergence of a new "disease" related to implants called siliconosis or "reactive silicone disease". However, this syndrome gained great repercussion only about a decade ago when it was described by Schoenfeld and Ahmon-Levin in a work published in 2011 called "'ASIA' – autoimmune/inflammatory syndrome induced by adjuvants" [1]. Watad et. al in his work on Shoenfeld Syndrome states that the appearance of autoimmune conditions is due to the interaction of a genetic predisposition and exposure to environmental factors resulting in a process of autoimmunity in the organism [19].

Reported in one of his articles that the silicone present in the prosthesis gel can oxidize into silica, causing the activity of the immune response to increase. The mechanism used to activate the immune and adaptive system consists of the activation of Th1 and Th17 and the release of interleukin 17, which will cause a response that will stimulate fibroblasts to produce fibrosis. This entire cytokine modulation mechanism explains one of the reasons for the cause of capsular contracture in autoimmune diseases. According to this capsular contracture can also be seen as one of the most frequent complications, almost always related to a deficient humoral system [10,11].

Several doctors and researchers began to correlate the symptoms presented by women with their respective silicone implants. For Unexplained symptoms such as fatigue, neurasthenia, myalgia, arthralgia, morning stiffness and night sweats are present in more than 60% of women. Furthermore, some patients presented cognitive problems, dermatological and gastrointestinal symptoms, alopecia and sleep disorders [5].

Mentions that: arthralgia was seen in approximately 61% of all cases. Chronic fatigue was present in 59% of the total. Myalgia in 49% of cases. Sleep disorders in 37%. General weakness was present in 33% and sicca symptoms in 18%. Fever was seen in 34% of patients, arthritis in 29% and neurological manifestations in 26%.

Demonstrates that in addition to the symptoms already mentioned, there is the possibility of association of connective tissue diseases such as Raynaud's Phenomenon, dermatomyositis, scleroderma and polymyositis with the silicone implant.

Highlights that in the work of it is reported that 30-50% of women who develop ASIA have Raynauld phenomenon. Furthermore, most patients presented anti-nuclear antibodies, in addition to other unspecified antibodies. The author also highlights that the implants act as adjuvants to induce local and systemic reactions triggered by macrophages and T cells that will produce antibodies and systemic symptoms [12-15].

Another fact mentioned by is that approximately 14 months after removal of the silicone implant, all symptoms improved or regressed, indicating a regression of the autoimmune reaction. Around 63% of women who underwent surgery to remove the silicone felt an improvement in symptoms such as myalgia, arthralgia, fatigue and neurological symptoms [14].

There is still great divergence in the literature regarding the time of onset of these symptoms. In general, studies show that symptoms begin 1 month to 39 years after silicone implant surgery. The work published by states that symptoms appear between 1 week and 60 months after implant surgery. Fegonilo, Cecci and Roccatelo suggest that the time interval between the placement of the prosthesis and the appearance of symptoms is approximately 2 years [12,16].

Regarding the diagnosis of ASIA, according to the study published by the diagnosis must be made based on major and minor criteria. It is organized as follows: either the fulfillment of 2 major criteria or a major and a minor criterion based on the Table 2 below, which was taken from the same study published in 2011

**Tabela 1.** Critérios sugeridos por Shoenfeld para o diagnóstico de ASIA

| Critérios maiores: |
|---|
| • Exposição a um estímulo externo (infecção, vacina, silicone, adjuvante) antes das manifestações clínicas. |
| • Aparecimento de uma das manifestações clínicas abaixo: |
| – Mialgia, miosite ou fraqueza muscular; |
| – Artralgia e/ou artrite; |
| – Fadiga crônica, sono não repousante ou distúrbios do sono; |
| – Manifestações neurológicas (especialmente associadas com desmielinização); |
| – Alteração cognitiva, perda de memória; |
| – Febre, boca seca; |
| • A remoção do agente iniciador induz melhora. |
| • Biópsia típica dos órgãos envolvidos. |
| **Critérios menores:** |
| • Aparecimento de autoanticorpos dirigidos contra o adjuvante suspeito. |
| • Outras manifestações clínicas (ex.: síndrome do cólon irritável). |
| • HLA específicos (ex.: HLA DRB1, HLA DQB1). |
| • Surgimento de uma doença autoimune (ex.: esclerose múltipla, esclerose sistêmica) |

Para o diagnóstico de ASIA: pelo menos a presença de dois critérios maiores ou um critério maior e dois menores.

Another disease with an increased incidence due to the increase in breast implants, in addition to having a better diagnosis, is BIA-ALCL, which is directly related to silicone, especially those with a textured capsule [17].

The pathogenesis of the disease is still not very clear, however, a higher rate of development of BIA-ALCL has been linked to textured capsule implants (this textured capsule was created in the 1960s as an alternative to reduce cases of capsular contracture, but the results are contradictory). One of the theories about the development of lymphoma is based on the formation of a subclinical biofilm, capsular contracture, repeated trauma, genetic predisposition or autoimmune etiology, related to ASIA, immunological response to the silicone components themselves were also considered. According to the 2019 Consensus Guidelines on the Diagnosis and Treatment of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL), there are no confirmed cases of the disease in patients with non-textured prostheses [7].

There are two courses of the disease, one being in situ, in which there is disease in the effusion or in the internal wall of the capsule. This course generally does not present a mass and can be confused with a benign seroma. There is also an infiltrative course, presenting with a palpable mass and affecting underlying tissues. This presentation has a worse prognosis (40% mortality in 2 years). Both presentations can present lymph node changes, and there are also cases of lymph node changes without other symptoms [7].

The symptoms of BIA-ALCL present as pain and breast asymmetry with a palpable mass, however its clinical features can be variable, with the presence of periprosthetic effusion, effusion with mass, isolated mass, with or without seroma or just lymph node involvement. The most common presentation is late effusion (48%-70% of cases), which can occur nine years after implantation. Therefore, any presentation of late effusion with rapid evolution, and which cannot be explained by infection or trauma, should be suspected of BIA-ALCL [7,18].

Any change in a silicone prosthesis must be investigated, always starting with a mammogram to look for a mass, liquid collection or lymph node enlargement - if this is not conclusive, an MRI can be requested. When a seroma or mass is found, a biopsy or fine needle aspiration should be performed. Other investigations that can be carried out are CD30 measurement and anaplastic lymphoma kinase, the first being positive and the second negative.

BIA-ALCL can manifest itself on average 8-10 years after the implant procedure, and when diagnosed, it is important to remove the complete capsule as soon as possible - a procedure performed by the plastic surgeon himself [18].

The cure for BIA-ALCL depends on the surgical removal of the prosthesis, with the capsule, and in cases infiltration of the affected underlying tissue (including lymph nodes according to staging). When correctly removed, there is a recurrence rate of 6%-11%, 0% for patients staged at T1 and 2, and 14.3% for stage 4. Survival is not affected by postoperative chemotherapy, and should removal of the contralateral prosthesis must be discussed (4.6% of cases are bilateral).

It is contraindicated to place a new prosthesis after identifying. Adjuvant treatments such as radiotherapy, chemotherapy and stem cell transplants have proven to be very effective and should be combined with surgery [7,19].

Outpatient follow-up is important after cure, being re-evaluated every 3-6 months for two years if there is no sign of recurrence, in the evaluations a tomography or PET scan can be performed [18].

**Conclusion**

Complications secondary to silicone implants are being increasingly studied and disseminated due to the increasing prevalence of this surgery. As mentioned in this article, ASIA and BIA ALCL are some of the main complications resulting from this procedure. However, although its pathophysiology is well elucidated in the literature, the symptoms and the time of onset of symptoms still do not have a standard, since several literatures differ in this regard, in addition to some authors placing

a very high time interval for the appearance initial. With regard to ASIA, it was noted that the most prevalent symptom is arthralgia, followed by chronic fatigue, resulting from the activation of the Th1 and Th17 immune system and the release of interleukin 17 - resulting in fibrosis from fibroblasts - , since the silicone present in the prosthesis gel can oxidize into silica, causing an increase in immune activity. In BIA ALCL, the most prevalent symptom is late stroke, with a period of symptomatic onset years after surgery - approximately 9 years -, in which after this onset the evolution occurs acutely. The pathophysiology of this complication occurs mainly with the development of seroma, being directly related to textured capsule implants, in addition to being related to the type of breast implant, genetic predisposition and the formation of a subclinical biofilm, making it necessary to evaluate the quality of the material used, as it can predispose the formation of this biofilm and lead to complications. Therefore, silicone implants can cause complications that affect the quality of life of patients, and attention should be paid to initial symptoms and seek medical help if any complications occur, regardless of the time interval, since the complications mentioned can occur many years later. carrying out the surgery [20].

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