

Immunological Abnormalities and Anaplastic Large Cell Lymphoma Associated with Breast Implant

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Abstract:

Numerous studies have explored the possibility of an association between breast implants and systemic symptoms potentially linked to exposure to silicone. Some studies show no direct association whereas others provide insufficient scientific evidence to prove or disprove an association. A number of investigators have explored the frequency and titers of antinuclear antibodies (ANAs) in women with or without signs and symptoms of illness and silicone (almost always gel-filled) breast implants. Also, breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) it is a rare form of lymphoma that occurs in some people who have had breast implants. This type of lymphoma occurs in the fluid and scar tissue (fibrous capsule) around the implant.

Key words: absent corpus callosum, Colpocephaly, fetal MRI, prenatal ultrasound

Introduction

There is a very high procedural demand for breast augmentation surgeries, the main indications being reconstruction after mastectomy, correction of congenital malformations, and cosmetic augmentation. While research on breast implant illness is not yet conclusive, there are some documented risks associated with breast implants. The U.S. Food and Drug Administration (FDA) has medical device reports (MDRs) for all types of implants regardless of their surface, filling, or shape. This means breast implant illness may affect those with silicone, saline, smooth, and textured implants¹.

Breast implant illness (BII) is a systemic complication associated with breast implants. A review of epidemiological studies in the past ten years exhibited evidence affirming an association between breast implants and autoimmune diseases. The most commonly recognized were Sjogren's syndrome, rheumatoid arthritis, systemic sclerosis, chronic fatigue syndrome, and Raynaud's syndrome. Explantation resulted in alleviation

of symptoms in over 50% of patients, strengthening the hypothesis linking breast implants to BII. Studies have shown that silicone is a biologically inert material and unlikely to be the cause of these symptoms. This is supported by the fact that increased risk of autoimmune disease was also reported in patients with other implantable biomaterials such as orthopedic implants².

Parallel to the myriad of symptoms associated with breast implants, increased risk of developing autoimmune disorders has also been implicated with breast implants³.

According to Watad et al., women with silicone breast implants were conclusively associated with a higher likelihood of autoimmune or rheumatic disorders diagnosis, regardless of whether the breast implant was placed for reconstructive or cosmetic reasons. When comparing women with silicone breast implants with matched breast implant-free

women, the hazard ratio of being diagnosed with at least one autoimmune/rheumatic disorder was 1.45 (95% CI 1.21-1.73), showing an increased risk of developing any autoimmune or rheumatic disorder in patients with breast implants⁴.

Case Report

A 45 year old female diagnosed with cutaneous lupus in 2017, with breast implant in 2012, presented in 2020 diffuse polyarthralgia. A

rheumatologist established the diagnosis of systemic lupus erythematosus based on positive autoantibodies (anti-Ro antibody, anti-La antibody) – and she received hydroxychloroquine 400mg/day.

In June 2023, she complained of pain and inflammation in her right breast (**Figure 1**).

A breast ultrasound was performed showing probably benign ultrasound changes with suspicion of right breast implant rupture.



Figure 1: Localized collection of inflammatory exudate in the breast tissue

Routine blood tests revealed leukocytosis, increased ESR (58 mm/h), raised C-reactive protein levels (12 mg/l). A breast MRI was performed: fluid collection in medium quantity arranged right periprosthetically, with

marked irregular gadolinophilic thickening of the posterior external capsule, with minimal intrathoracic extension through the adjacent intercostal spaces, with invasion of the epipleural fatty space (**Figure 2**).

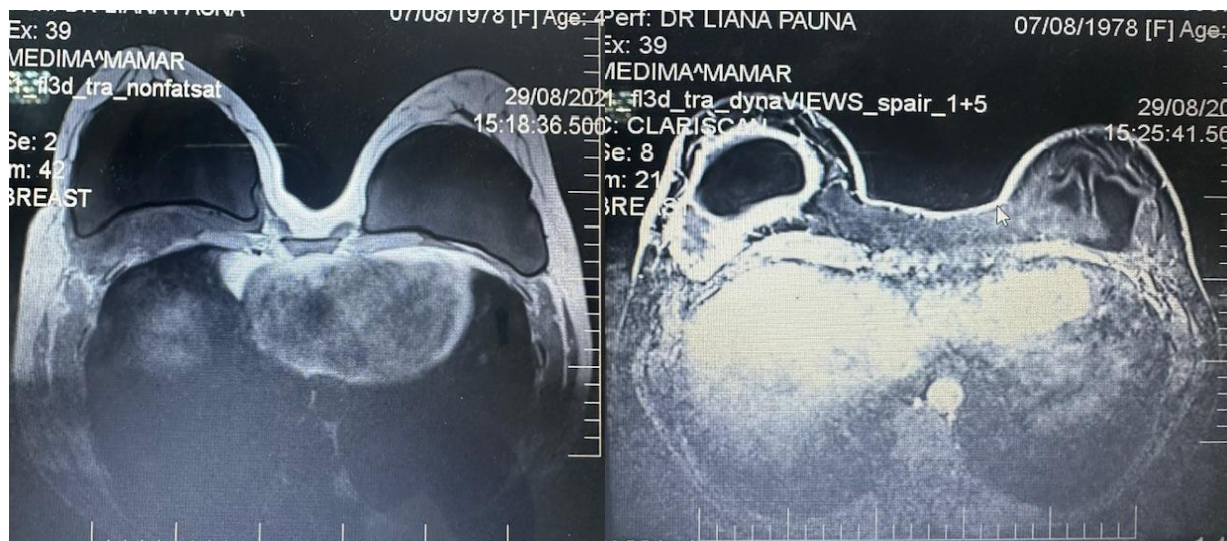


Figure 2: Fluid collection in medium quantity arranged right periprosthetically

Biopsy of this collection and IHC tests established the histological diagnosis of anaplastic large cell lymphoma -ALK1 negative and CD30 positive (**Figure 3**).

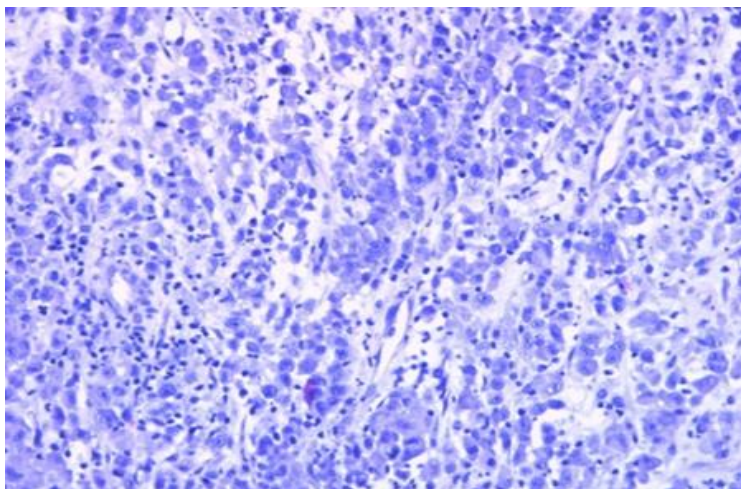


Figure 3.1: Malignant tumor proliferation composed of large cells with marked pleomorphism and pleomorphic nuclei with prominent nucleoli and atypical mitoses- H&E stain (20x objective)

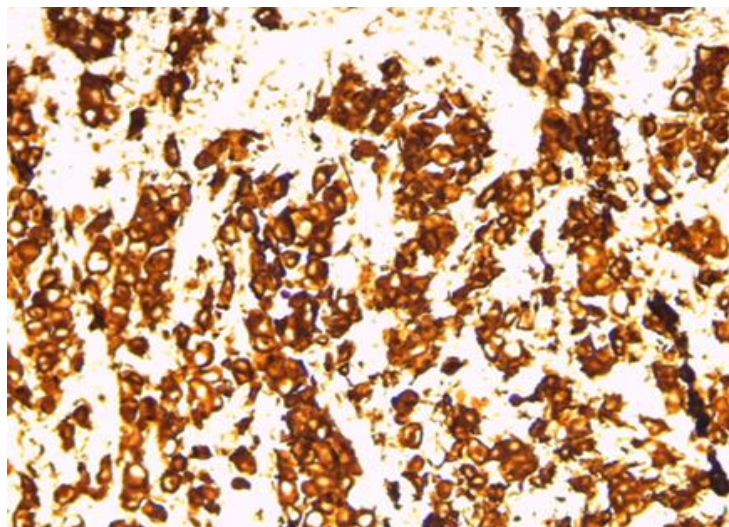


Figure 3.2: Tumor cells with intense positive membrane staining for CD30 (20x objective). Immunohistochemistry, clone BerH2, Ventana BenchMark ULTRA automated system, OptiView DAB IHC Detection Kit.

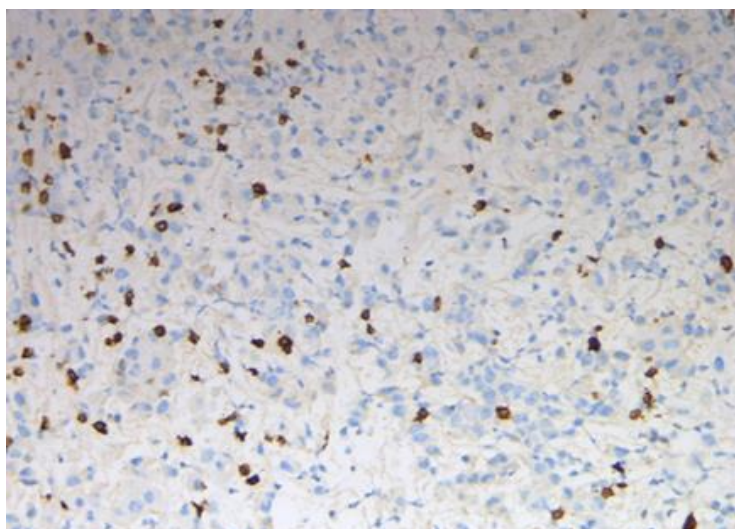


Figure 3.3: Tumor cells with weak focal positive membrane staining for CD3 (20x objective). Immunohistochemistry, clone L26, Ventana BenchMark ULTRA automated system, OptiView DAB IHC Detection Kit.

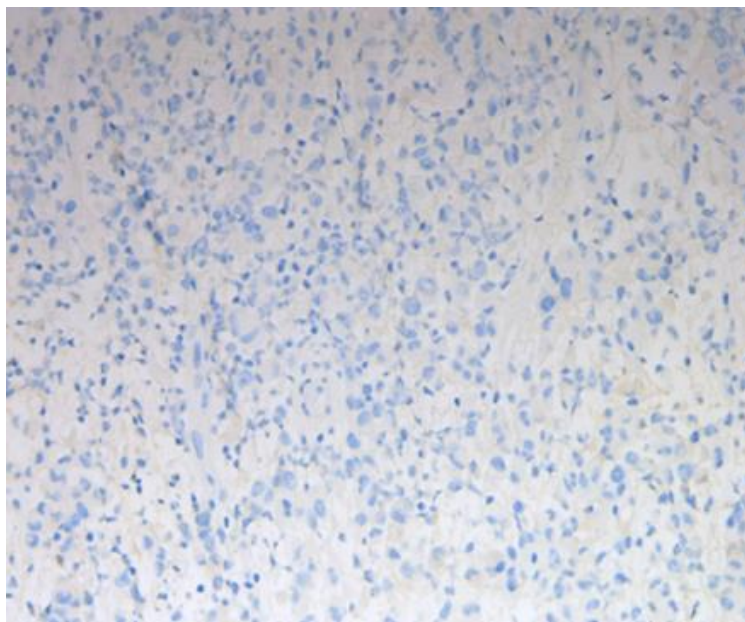


Figure 3.4: Tumor cells with absent staining for ALK1 (20x objective). Immunohistochemistry, clone ALK01, Ventana BenchMark ULTR automated system, OptiView DAB IHC Detection Kit.

PET/CT reveals active metabolic changes located around prosthetic implant in the right breast (**Figure 4**).



Figure 4: Active metabolic changes located around prosthetic implant in the right breast on PET/CT

In october 2023, a commission composed of general surgery, plastic surgery and thoracic surgery decided to perform surgery to remove the tumor and breast prosthesis. (**Figure 5.A, 5.B**)

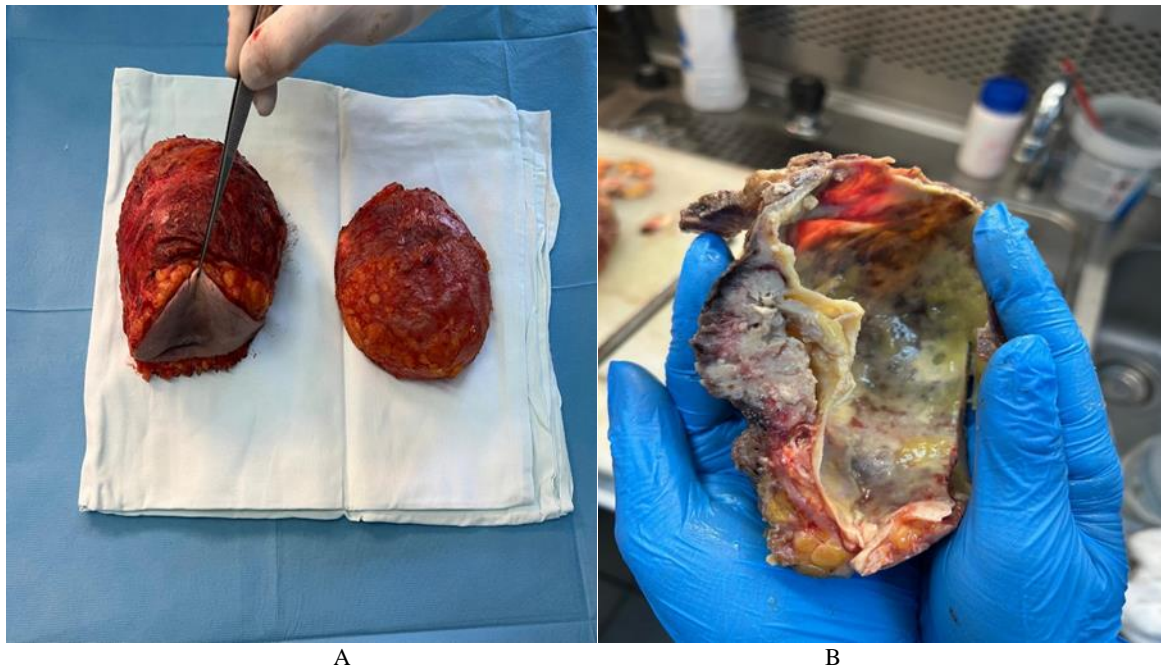


Figure 5.A- Intraoperative image of the en bloc specimen of the tumor, **B-** a section through the tumor mass

In november 2023, she presents for the Rheumatology department in our hospital for medical evaluation. Clinical examination revealed good general condition, no rheumatological symptoms, post-surgical scars after explantation (**Figure 6**).



Figure 6: Post surgical scars after explantation

Blood tests showed no signs of inflammation, renal and hepatic function was normal, rheumatoid factor negative, normal complement, ANA antibody 3.9 ui/ml, anti-Ro antibody 107 ui/ml.

The ophthalmological consultation revealed a positive Schirmer test.

Considering the patient's history of positive autoimmune markers, high titer anti-Ro antibodies, positive anti-La titer, and positive Schirmer test,

it was decided to perform a salivary gland biopsy in order to confirm or rule out Sjogren's Syndrome.

The salivary gland biopsy showed fragments of squamous mucosa and salivary glandular acini with mild fibrosis and minimal inflammatory lymphoplasmacytic infiltrate, but no histological criteria suggestive of Sjogren's Syndrome (**Figure 7**).

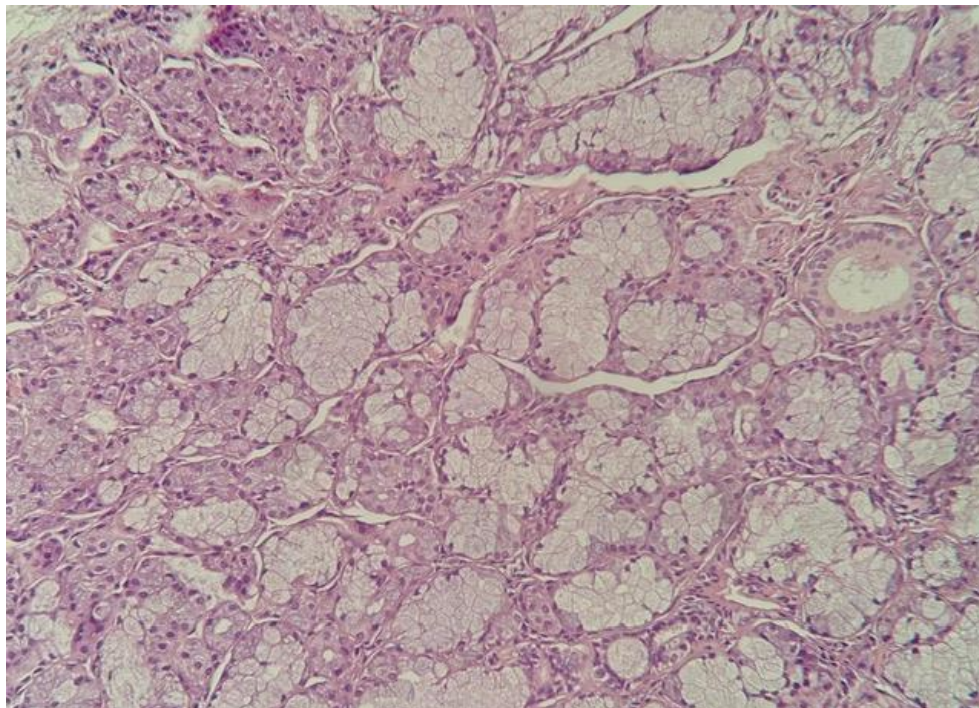


Figure 7: Minor salivary gland tissue showing rare scattered lymphocytes with no aggregate formation, corresponding to a Focus Score <1

Corroborating all of this data, the patient does not meet the criteria for systemic lupus erythematosus or Sjogren's Syndrome.

Reading the data from the literature, it has been observed that breast implant patients can develop positive antibodies (especially anti-Ro, anti-La), due to exposure to the silicone of the implant. Repeating antibodies after 6 months of explantation will clarify this aspect.

In November 2023, chemotherapy for anaplastic large cell lymphoma is started with brentuximab, cyclophosphamide, doxorubicin which has been well tolerated (6 cycles). At the same time, hydroxychloroquine was stopped.

In March 2024, FDG PET/CT showed no residual active metabolic damage and a favorable response to oncological treatment (**Figure 8**).

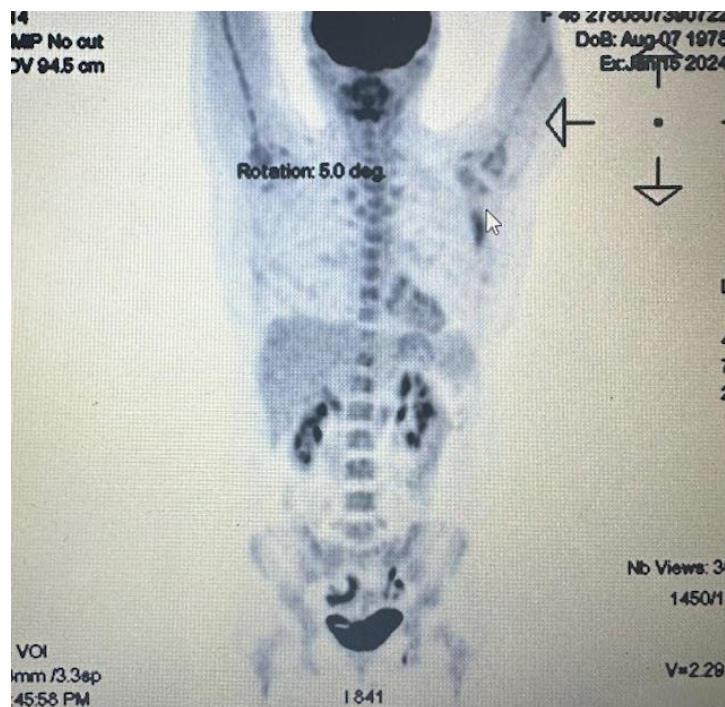


Figure 8: PET/CT showing no residual active metabolic damage

In June 2024, an abdominal MRI was performed, without notable particularities in the oncological context (**Figure 9**).

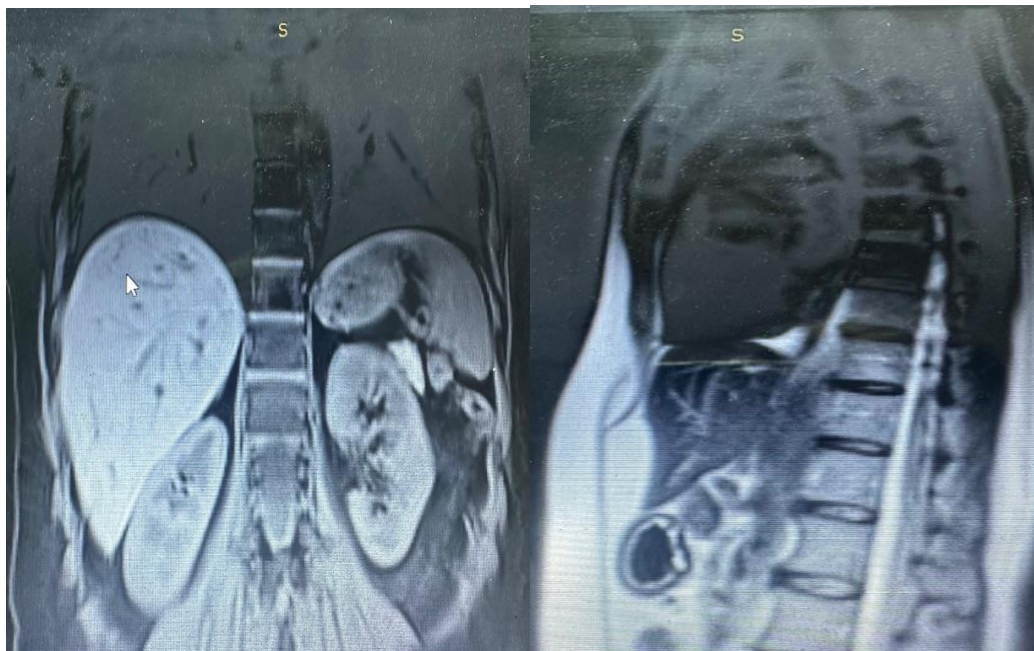


Figure 9: Abdominal MRI

In July 2024 (8 months after chemotherapy and explantation of breast implants) antibodies have been repeated: ANA antibody 3.2 ui/ml, anti-Ro antibody 34 ui/ml, anti-La antibody negative. Clinically, the patient is in good general condition, without skin lesions suggestive of lupus,

without arthralgia, and denies xerostomia. She complains of paresthesia (likely in the context of chemotherapy). Biologically, no inflammatory syndrome detected (**Figure 10**).



Figure 10. Good evolution of breast implant

Discussion

Considering the decrease in antibody titer following the implant removal and lymphoma treatment, we concluded that immunological reactions in women with implants are more common and might result from exposure to silicone breast implants.

Following a thorough review of the literature, we reached the conclusion that despite the ongoing concerns about breast implant illness (BII),

previous research has not definitively shown a connection^{5,6,7,8,9}. A systematic review from 86 studies on five health-related databases (PubMed, EMBASE, MEDLINE, CINAHL Complete and EBM-Reviews) from 2021 aimed to evaluate the risk of rheumatic disease such as systemic sclerosis (SSc), Sjogren syndrome (SS), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), fibromyalgia and also evaluated self-reported symptoms such as arthralgias, myalgias, sicca and Raynaud's phenomenon. The review based on small number of studies,

showed an increase incident of scleroderma and rheumatoid arthritis that could not be excluded, but further studies need to be done to confirm the risk of developing a rheumatic disease secondary to breast implants. It is important to note that among studies that evaluate patients after breast implants removal, it was uncertain if the improvement attributed to explantation is a result of removal of the breast implants or if they are linked to the use of glucocorticoids or other immunosuppressive drugs, the natural course of the disease, or a placebo effect¹⁰.

Research in this domain will pave the way for rigorous protocols and more frequent antibody screening in such cases.

The association between breast implants and anaplastic large-cell lymphoma was approved (BIA-ALCL). The Food and Drug Administration (FDA) has received a total of 1264 reports of BIA-ALCL cases from worldwide as of June 30, 2023¹¹. BIA-ALCL is a rare type of T-cell non-Hodgkin lymphoma that is characterized by being CD30 positive and lacking anaplastic lymphoma kinase (ALK). The exact cause of the cancer is yet fully understood, but it is believed that chronic inflammation may play a role in the development of the cancer. Most cases are identified around 7 to 10 years post-implantation. Symptoms may include breast swelling, pain, asymmetry, skin changes, swollen lymph nodes, and systemic symptoms. A fine-needle aspiration or biopsy will confirm the diagnosis by showing the CD30 and epithelial membrane antigen positivity. Complete surgical removal at the T1-T3 stages can result in a cure for BIA-ALCL¹².

Conclusions

Autoimmune/inflammatory syndrome by adjuvants (ASIA), allergies, autoimmune diseases, immune deficiencies and lymphomas can occur in patients with silicone breast implants. There is a need for adequately adjusted epidemiological studies to ascertain the frequency of these diseases. Explantation of the breast implants, however, should be advised to patients with complaints, as 60–80% of patients experience improvement in signs and symptoms after explantation¹³.

A multidisciplinary approach (Rheumatology, Pathology, General Surgery, Plastic Surgery) is crucial for the proper management of this condition and antibody screening would be required before breast implant.

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