

# Breast Implant–Associated Anaplastic Large-Cell Lymphoma: Why Must We Learn About It?

Letícia Morais Coelho de Oliveira Sermoud, MD<sup>1</sup>; Sérgio Romano, MD<sup>2</sup>; Maurício Chveid, MD<sup>3</sup>; and Gilberto Luiz da Silva Amorim, MD<sup>1</sup>

abstract

Breast implant–associated anaplastic large-cell lymphoma (BIA-ALCL) is a rare, breast implant–associated T-cell lymphoma in which CD30 is expressed and anaplastic lymphoma kinase (*ALK*) expression is absent. However, despite the low risk of developing the disease, more information on BIA-ALCL is necessary, because the number of women with breast implants has been increasing worldwide; Brazil is one of the main markets for this type of implant. The objectives of this review are to clarify the issue of BIA-ALCL occurrence after risk-reducing mastectomy, to show the importance of this disease, and to raise awareness among the medical community about this rare pathologic condition. In 2016, BIA-ALCL was included by WHO in the new classification of lymphomas, and this demonstrates the attention that medical entities should give to this disease. Thus, awareness about BIA-ALCL must be broadened among the medical societies and regulatory authorities, both to foster better approaches to this disease, which should be evaluated in a multidisciplinary manner, and to provide better knowledge among health care professionals and the target population about the use of implants.

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## INTRODUCTION

Breast implant-associated anaplastic large-cell lymphoma (BIA-ALCL) is a rare, breast implant–associated T-cell lymphoma in which CD30 is expressed and anaplastic lymphoma kinase (*ALK*) expression is absent.<sup>1</sup> According to the American Society of Plastic Surgeons, more than 296,000 aesthetic breast procedures and approximately 93,000 breast-reconstructing procedures were conducted in the United States in 2010.<sup>2</sup> According to the International Society of Aesthetic Plastic Surgery, in 2016, Brazil held the second position behind the United States, with 434,775 breast implant operations. In 1997, Keech and Creech<sup>3</sup> described the first case of BIA-ALCL, and the first epidemiologic study was published in 2008.<sup>4</sup> Recently, in 2016, after a review and update by WHO, this disease was included in the Classification of Lymphoid Neoplasms and was acknowledged as a new pathologic condition.<sup>5</sup>

BIA-ALCL can manifest as a periprosthetic fluid collection (seroma) or mass and occurs between 8 and 10 years after implantation of an aesthetic or reconstructive breast prosthesis after surgery for breast carcinoma.<sup>6,7</sup> The most common symptom is seroma, and such occurrences should be cytologically analyzed when they are late (ie, more than 1 year after the implant procedure has been conducted).<sup>8</sup>

To make the diagnosis, imaging tests—such as breast ultrasound; nuclear magnetic resonance; and, in selected cases, positron-emission tomography (PET)—should be conducted. The periprosthetic liquid should be evaluated via fine-needle aspiration puncture and be sent for cytologic analysis, and tissue biopsy samples of the suspected mass preferably should be evaluated by a hematopathologist.<sup>6</sup> Immunohistochemical analysis is paramount to reveal overexpression of CD30<sup>8</sup> and absence of *ALK*.<sup>4</sup>

In a study published in 2008, between 100,000 and 300,000 Dutch women with breast implants were assessed. The incidence of BIA-ALCL ranged from 0.1 to 0.3 per 100,000 women with implants per year.<sup>4</sup> Despite the low risk of developing the disease,<sup>4</sup> greater understanding of BIA-ALCL is of interest for women, oncologists, mastologists, plastic surgeons, regulatory agencies, and the general public, because the number of women with breast prosthetics has been increasing worldwide. Moreover, Brazil is one of the main markets for this type of implant.

The objectives of this review are to clarify the issue of BIA-ALCL that occurs after risk-reducing mastectomy, to show the importance of this disease, and to raise awareness among the medical community about this rare pathologic condition.

Author affiliations and support information (if applicable) appear at the end of this article.

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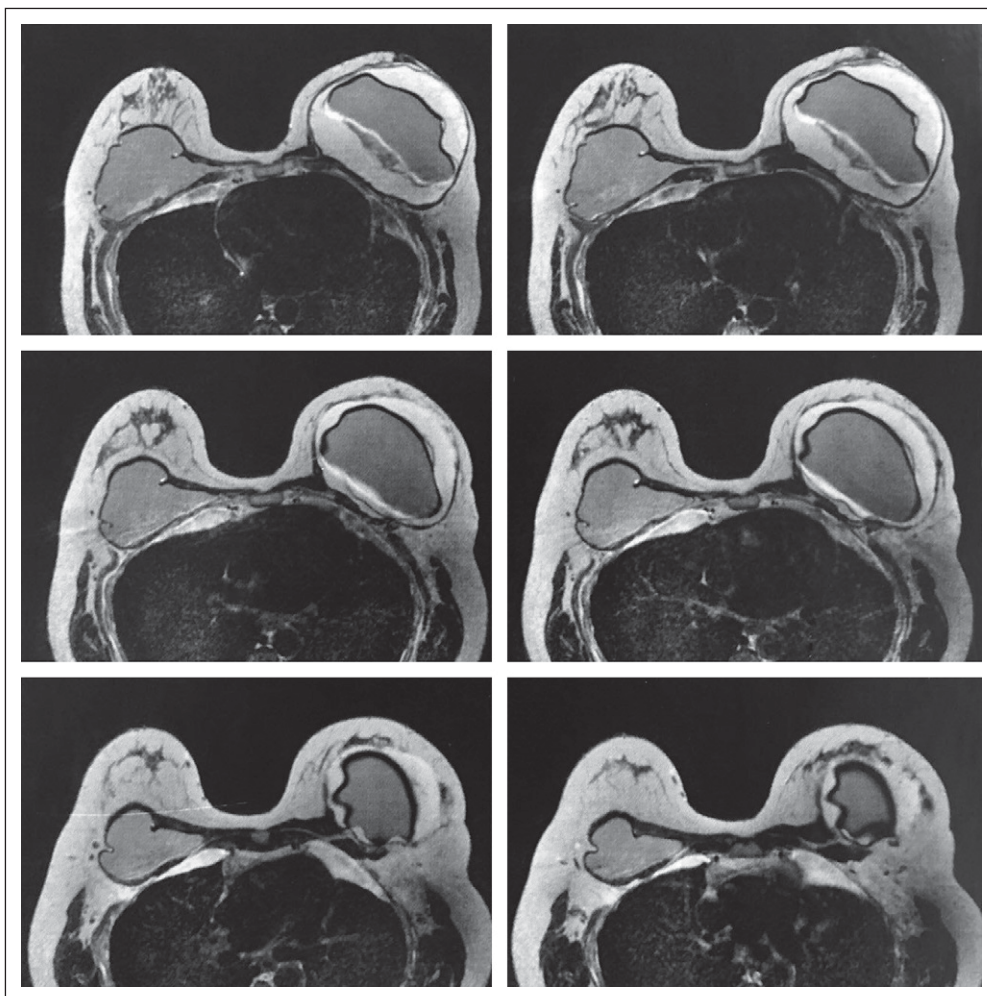
## CASE PRESENTATION

The patient was a 53-year-old woman with history of risk-reducing mastectomy and implantation of a texturized silicone prostheses in 2009. The risk-reducing surgery was an elective procedure: the patient had a positive family history of breast neoplasia (two aunts on her father's side) but no assessments of *BRCA1* and *BRCA2* mutation. In 2015, she presented with the first evidence of seroma and underwent a puncture procedure. There was a recurrence of seroma in 2017, and two puncture procedures were performed, in which between 250 and 400 mL of liquid was removed, initially without any cytopathologic analysis. Because her condition persisted, she sought another mastologist.

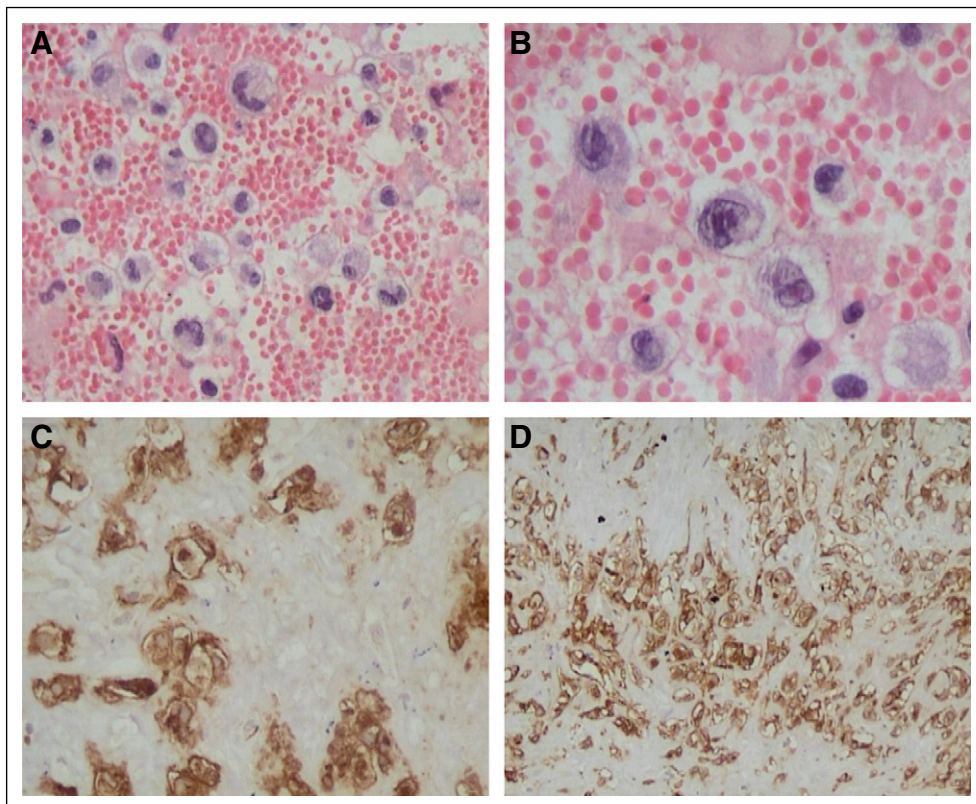
During the physical examination, her breast presented as bulging with unilaterally increased volume. Breast ultrasound was conducted and showed a large accumulation of periprosthetic liquid. Nuclear magnetic resonance (Fig 1) showed a thick capsule and an accumulation of debris, which presented as an estimated intracapsular volume of

500 mL; the muscle plane and axillary lymph nodes did not show any abnormalities. On December 7, 2017, removal of the implant was indicated, and total capsulectomy was performed; the procedure included removal of the tumor that was found. The histopathologic report showed that an infiltration of anaplastic epithelial cells had occurred, with irregular hyperchromatic nuclei and vacuolated cytoplasm organized in strings or small nests, compatible with poorly differentiated carcinoma. The immunohistochemical evaluation was positive for CD30, CD3, and CD4; negative for CD8 and CD20; and negative for *ALK*. This corroborated the diagnosis of BIA-ALCL (Fig 2). No sentinel lymph node biopsy was performed. PET-computed tomography did not indicate any disease at distant sites.

No adjuvant treatment was indicated. The patient continues to undergo periodic follow-up at the clinical oncology and mastology clinics and was without any evidence of disease at the last check-up, which was conducted in December 2018.



**FIG 1.** Nuclear magnetic resonance image (transversal plane) showing a peri-implant seroma.



**FIG 2.** (A and B, upper) Hematoxylin and eosin staining: hallmark cells with irregular nuclei (kidney-shaped nuclei) and abundant eosinophilic cytoplasm. (C and D, lower) Immunohistochemical staining: CD30-positive tumor cells.

### EPIDEMIOLOGY

BIA-ALCL is a rare type of non-Hodgkin lymphoma that has seldom been described in the worldwide medical literature. In Brazil, few reports on this disease have been published. However, given the increasing numbers of breast implant procedures that are being conducted both for aesthetic and reconstructive purposes, greater dissemination of information about this disease is paramount.

The patient of this case study was 53 years old when the diagnosis was made, which is the median age found in the medical literature.<sup>9</sup> A population-based evaluation conducted in the Netherlands showed that, among 32 patients analyzed, only three had had breast implants after prophylactic mastectomy, which was the cause described for the patient of this case study. However, the main indication of BIA-ALCL has been aesthetic, with 22 such cases reported in the study by de Boer et al.<sup>10</sup>

### DIAGNOSIS

According to Leberfinger et al,<sup>11</sup> in a systematic review in 2017, 66% of the evaluated patients presented with seroma—the same presentation found in this case study. It is important to highlight that, in patients who present with late seroma and persistent peri-implants, the possibility of BIA-ALCL must be considered.<sup>12,13</sup> An official document

that was developed after a meeting between some Italian medical associations specified that patients with late seroma (ie, those that occurred at least 6 months after implantation) and cold seroma (ie, those negative for histories of trauma and infections) should be evaluated with consideration of BIA-ALCL as a diagnosis.<sup>14</sup> It is also known that patients with periprosthetic accumulations of fluid present better prognoses than do those diagnosed with solid masses, which seem to have more aggressive behavior.<sup>15</sup> In addition to the mass adjacent to the implant, capsular contracture may be found in some patients.<sup>13</sup> According to de Boer et al,<sup>10</sup> the median interval between breast implantation and the diagnosis of BIA-ALCL was 13 years, whereas it was 8 years according to Xu et al.<sup>7</sup> In the case elucidated here, the interval was also 8 years.

### STAGING

According to the criteria of the National Comprehensive Cancer Network (NCCN), our case study observed a patient with stage IA (T1N0M0) disease. According to Campanale et al,<sup>14</sup> in a study of 22 Italian patients, 15 presented with stage IA disease, and two presented with T4 (locally invasive tumor beyond the capsule) disease. Two staging systems have been used to analyze BIA-ALCL: Ann Arbor for lymphomas and TNM for solid tumors. In the Ann Arbor system, stage IE is defined as disease that is limited to single



extranodal sites, such as breasts or only the capsular envelopment; stage IIE is defined as a disease with local lymph node dissemination.<sup>6</sup> However, the rate of occurrence of stage I BIA-ALCL, according to the Ann Arbor staging system, was more than 80%, which does not adequately divide the various prognostic groups.<sup>1</sup> Therefore, in 2016, Clemens et al<sup>1</sup> proposed a surgical and pathologic staging system for BIA-ALCL based on the TNM system for solid tumors, for which the latest update by the NCCN was in 2019.<sup>16</sup> This staging is divided as follows: IA (T1N0M0), IB (T2N0M0), IC (T3N0M0), IIA (T4N0M0), IIB (T1-3N1M0), III (T4N1-2M0), and IV (any T, any N,M1)—in which T1 refers to confined to seroma; T2, discrete capsule infiltrate; T3, cell conglomerate or massive capsule infiltrate; T4, infiltration beyond the capsule; N0, without lymph node involvement; N1, one affected regional lymph node; N2, multiple affected regional lymph nodes; M0, not spreading to distant sites; and M1, spreading to distant sites.<sup>16</sup> Also in the same study, the TNM staging system for solid tumors showed the ability to predict the overall survival of the patients with BIA-ALCL more precisely than did the Ann Arbor lymphoma system. Moreover, it predicted the prognosis and treatment regimen for patients with BIA-ALCL.<sup>1</sup>

### TREATMENT AND FOLLOW-UP

According to the NCCN guidelines, BIA-ALCL that is confined to the capsule can only be treated, in most cases, through surgical intervention. Cases with residual disease or incomplete resection must be evaluated with regard to adjuvant radiotherapy treatment. Also, chemotherapy should be encouraged in patients with lymph node involvement and/or disease at distant sites.<sup>6</sup> In the study conducted by Campanale et al,<sup>14</sup> the systemic treatment most used were the following: CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), in most cases; CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone); DHAP (dexamethasone, cytarabine at high doses, and cisplatin); and brentuximab vedotin (monoclonal antibody directed toward the protein CD30), which was used in one patient of the 22 patient cases evaluated. It has been recommended that the follow-up for these patients during the first 2 years after surgery should consist of clinical examinations every 3 to 6 months and PET-computed tomography every 6 months.<sup>17</sup>

### AFFILIATIONS

<sup>1</sup>Oncologia D'Or, Rio de Janeiro, Brazil

<sup>2</sup>Brazilian National Cancer Institute and Microimagem Pathology Laboratory, Rio de Janeiro, Brazil

<sup>3</sup>Private Breast and Plastic Surgeon, Rio de Janeiro, Brazil

### CORRESPONDING AUTHOR

Letícia Morais Coelho de Oliveira Sermoud, MD, Department of Medical Oncology, Oncologia D'or, Avenida das Américas, 3500 Barra da Tijuca, Rio de Janeiro, RJ CEP 22640-102 Brazil; e-mail:leticiamoraisco@gmail.com.

### WHY WE MUST DISCUSS BIA-ALCL?

In 2014, Xu et al<sup>7</sup> had already reported the importance of acknowledging BIA-ALCL as a new pathologic condition. In 2016, it was included by WHO in the new classification of lymphoid neoplasms.<sup>5</sup> This shows the attention that medical entities should give to this disease. It is necessary to inform patients about the possibility of occurrence of this condition before the implant procedure is conducted,<sup>13</sup> even though the risk of developing the disease is known to be low. It should be noted that, after the implant has been placed, it is not necessary to change the medical follow-up routine.<sup>13</sup>

In addition to the need to provide greater information for the patients involved, studies like this case study should be encouraged to increase dissemination of knowledge about the disease among medical communities. In this regard, the United States created the Patient Registry and Outcomes for Breast Implants and Anaplastic Large Cell Lymphoma Etiology and Epidemiology (PROFILE registry), in which all occurrences of BIA-ALCL should be recorded.<sup>15,18</sup> A study published in 2019 reported that a total of 186 patient cases of BIA-ALCL occurred in the United States between 2012 and 2018 and concluded that the PROFILE registry was an essential tool to unify data that related to BIA-ALCL.<sup>19</sup> Other countries, such as Australia, France,<sup>13</sup> Italy,<sup>14</sup> and England,<sup>15</sup> also have made registration of these patient cases in the respective regulatory authorities mandatory.

Thus, awareness of BIA-ALCL must be broadened among medical societies and regulatory authorities, both for a better approach toward this disease, which should be evaluated in a multidisciplinary manner, and for better knowledge among health care professionals and the target population about the use of implants. Therefore, it is important to create public policies to record new occurrences, and there is a need for future studies to increase the knowledge about this rare pathologic condition. Under any circumstances, the hypothesis of BIA-ALCL should be raised for every patient who presents with recurrent late seroma.

### AUTHOR CONTRIBUTIONS

**Conception and design:** Letícia Morais Coelho de Oliveira Sermoud, Gilberto Luiz da Silva Amorim

**Collection and assembly of data:** Letícia Morais Coelho de Oliveira Sermoud, Maurício Chveid, Gilberto Luiz da Silva Amorim

**Data analysis and interpretation:** Letícia Morais Coelho de Oliveira Sermoud, Sérgio Romano, Gilberto Luiz da Silva Amorim

**Provision of study material or patients:** Letícia Morais Coelho de Oliveira Sermoud, Sérgio Romano, Maurício Chveid, Gilberto Luiz da Silva Amorim

**Manuscript writing:** All authors

**Final approval of manuscript:** All authors

**Agree to be accountable for all aspects of the work:** All authors

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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**Gilberto Luiz da Silva Amorim**

**Honoraria:** Roche, Novartis, Lilly, Sanofi, Aventis

**Consulting or Advisory Role:** Novartis, Roche

**Travel, Accommodations, Expenses:** Roche

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