CASE REPORT
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BREAST IMPLANT-ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA IN LI-FRAUMENI SYNDROME: CASE-BASED LITERATURE REVIEW

Linfoma anaplásico de grandes células associado a implante na síndrome de Li-Fraumeni: relato de caso baseado em revisão de literatura

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ABSTRACT

Breast implant-associated anaplastic large cell lymphoma is a rare disease related to chronic seroma around breast implants. Breast implant-associated anaplastic large cell lymphoma has been recently recognized by the World Health Organization as a type of T-cell non-Hodgkin lymphoma of the breast. The main features comprise chronic seroma which develops a year posterior to breast surgery, with symptoms such as breast pain, swelling, skin hyperemia and a nodule or mass of the breast. Li-Fraumeni Syndrome is associated with germline *TP53* mutation and enhances the risks of developing many types of cancers, including breast and hematologic malignancies. We report a case of a 56-year-old female with Li-Fraumeni Syndrome and a history of breast cancer who underwent a mastectomy to treat breast cancer and prophylactic contralateral nipple-sparing mastectomy followed by bilateral breast implant reconstruction with textured silicone implants. This patient developed Breast implant-associated anaplastic large cell lymphoma seven years later. A literature review on multidisciplinary approach to this condition was performed.

KEYWORDS: lymphoma; Li-Fraumeni syndrome; breast implants; breast cancer; anaplastic large cell lymphoma.

RESUMO

O linfoma anaplásico de células grandes associado ao implante mamário é uma doença rara relacionada ao seroma crônico em torno dos implantes mamários. O linfoma anaplásico de células grandes associado ao implante foi recentemente reconhecido pela Organização Mundial de Saúde como um tipo de linfoma não-Hodgkin de células T da mama. As principais características incluem o seroma crônico que se desenvolve um ano depois da cirurgia da mama, com sintomas como dor na mama, inchaço, hiperemia da pele e um nódulo ou massa da mama. A síndrome de Li-Fraumeni está associada à mutação da linha germinativa no TP53 e aumenta o risco de desenvolvimento de muitos tipos de câncer, incluindo neoplasias mamárias e hematológicas. Relatamos um caso de uma mulher de 56 anos de idade com Síndrome de Li-Fraumeni e um histórico de câncer de mama submetido a uma mastectomia para tratar câncer de mama e mastectomia profilática contralateral poupadora de mamilo seguida de reconstrução bilateral de implantes mamários com implantes de silicone texturizados. Esta paciente desenvolveu linfoma anaplásico de células grandes associado ao implante mamário sete anos depois. Foi realizada uma revisão da literatura sobre uma abordagem multidisciplinar para essa condição.

PALAVRAS-CHAVE: linfoma; síndrome de Li-Fraumeni; implantes de mama; neoplasias da mama; linfoma anaplásico de células grandes.

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INTRODUCTION

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a rare form of T-cell non-Hodgkin lymphoma of the breast. The first case was reported by Keech and Creech[1] in 1997 and only in 2016 the World Health Organization (WHO) classified it as a new type of lymphoid neoplasm[2]. This recent recognition was important to allow specific recommendations for treatment of this disease.

Doren et al.[3] reported that lifetime prevalence of BIA-ALCL was approximately 1 in 30,000 for women with textured implants. Other series estimate lifetime risk range from 1:1000 to 1:10,000 in women with textured implants[4]. Up to date, more than 500 cases of BIA-ALCL have been confirmed worldwide[5]; nevertheless, the exact incidence is difficult to define due to unfamiliarity with this new entity.

Li-Fraumeni syndrome (LFS) is a cancer predisposition syndrome caused by germline mutations in *TP53* gene, associated with a high lifetime risk of multiple types of cancer[6-8]. In adults, LFS tumor spectrum is dominated by pre-menopausal breast carcinomas and soft-tissue sarcomas[6-8]. In LFS patients, there are no data available on increased risk of BIA-ALCL compared to non-carriers of *TP53* gene mutation.

The aim of this study is to report a case of BIA-ALCL in a patient with LFS that presented breast swelling associated with chronic seroma around the implant with adjacent mass, seven years after breast surgery, and to perform a literature review on the multidisciplinary approach to this condition.

CASE REPORT

A 56-year-old white female carrier of LFS underwent left radical modified mastectomy in 2009 due to Paget's Disease associated with ductal microinvasive carcinoma, and right risk reduction nipple-sparing mastectomy followed by bilateral breast implant reconstruction with textured silicone implants. Seven years later, she reported right-sided recurrent breast swelling that had started 18 months before. A magnetic resonance image (MRI) of the breast showed moderate fluid collection surrounding the right implant, with focal capsular nodules, peripheral enhancement and right axillary lymph node with cortical thickening. Fine needle aspiration cytology (FNAC) was negative for carcinoma.

The following year, patient manifested skin hyperemia around the right nipple-areolar complex (NAC). Breast ultrasound revealed a circumscribed hypoechogenic mass adjacent to the breast implant, without fluid collection, localized in the low-inner quadrant (LIQ), associated with a right axillary lymph node with cortical thickening. An MRI showed a 6 cm heterogenous mass with peripheral peri-prosthesis contrast enhancement, NAC enhancement and enlarged ipsilateral axillary lymph nodes (Figure 1).

A core-biopsy of the mass revealed eosinophilic infiltration of the fibrous tissue of the capsule, interspersed with atypical lymphoid cells (hematoxylin and eosin), which showed strong and diffuse expression of CD 30 and P53 protein, and no expression of ALK (immunohistochemistry). The right axillary lymph node FNAC presented atypical lymphoid cells. These findings confirmed BIA-ALCL diagnosis.

Staging positron emission tomography (PET-CT) detected enhanced metabolic activity only in the right breast (Figure 2). The patient underwent surgical treatment with excision of the right mass, ipsilateral lymph node axillary dissection and bilateral implant removal (Figure 3). Adjuvant treatment was not necessary.

DISCUSSION

Primary breast lymphomas are rare, accounting for 0.04–0.5% of all breast cancers and less than 10% of them are of T-cell origin[5]. BIA-ALCL is a subset of T-cell lymphoma of the breast with a typical indolent progression[9]. On average, diagnosis is made over 7 to 10 years after breast implantation[4,10].

Theories explaining the etiology of BIA-ALCL encompass a correlation between chronic T-cell stimulation due to Gram-negative bacteria, chronic seroma around textured implants and host genetics in genetically susceptible patients[2,5]. These data are supported by the evidence that a higher number of T-cells have been found around textured breast implants with a high bacterial load in patients with BIA-ALCL, associating the bacterial antigen stimulation with the chronic inflammation produced by the textured implants[11].

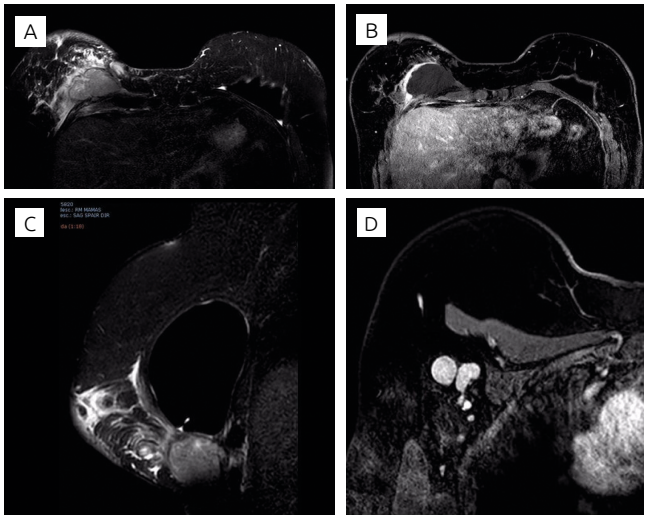

Figure 1. Magnetic Resonance Image (MRI) revealed a (A, B, C) 6 cm heterogenous mass in the junction of the inferior quadrants, with peripheral contrast enhancement, NAC enhancement and (D) enlarged ipsilateral axillary lymph nodes.

In a series of 55 patients from Australia and New Zealand, all cases of BIA-ALCL had exclusively occurred in textured implants[10]. The hypothesis for this relationship is that textured implants have a greater surface area and rough interface, which enhances bacterial adhesion and biofilm burden, triggering a T-cell clonal expansion[10,11].

BIA-ACLC is a CD30+, ALK negative lymphoma[9]. Pathological findings report atypical cells, interspersed in an eosinophil background, and immunophenotype reveals a diffuse expression of CD30 and negative ALK in malignant cells[12,13]. In addition, a somatic mutation of TP53 protein was described in BIA-ALCL[4], consistent with the case reported.

Li-Fraumeni syndrome (LFS) is an autosomal-dominant genetic disorder inherited by means of *TP53* mutations. From LFS patients listed in the International Agency for Research on Cancer (IARC) germline TP53 database, 2,550 different tumors are documented and only 4.7% of these tumors are hematological neoplasias[7], including lymphoid and myeloid leukemia, myelodysplastic syndrome and, to a lesser extent, lymphoma[8]. Also, the risk of breast cancer in LFS patients exceeds the risk of lymphoma. Analysis of LFS carriers by the National Cancer Institute (NCI) revealed a cumulative incidence rate of 54% by age 70 for breast cancer among female carriers[14].

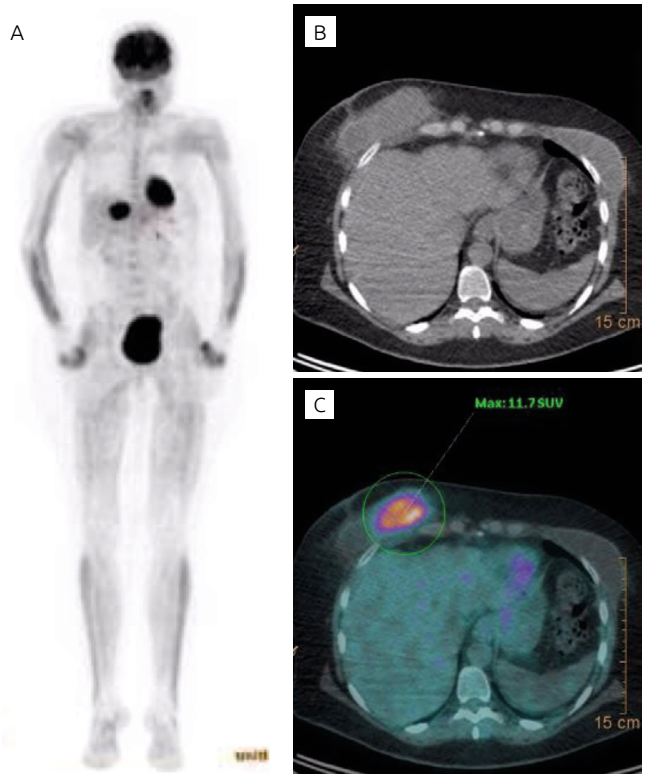

Figure 2. Staging positron emission tomography (PET-CT) detected enhanced metabolic activity only in the right breast with a standard uptake value=11,6. (A) Coronal maximum intensity projection image; (B) axial nonenhanced CT image; (C) axial PET-CT fused image.

Despite unavailable data of increased risk of BIA-ALCL in LFS patients, the literature reports a case relating BIA-ALCL in a LFS patient[15]. In Brazil, the incidence of *TP53* mutation in southern and southeastern Brazil is higher than worldwide[16]. We report a second case linking BIA-ALCL and LFS.

BIA-ALCL most often presents seroma around the breast implant (60-80%) with a variable volume of 20–1,000 mL and may manifest with breast pain, swelling, skin hyperemia or asymmetric capsular contracture[2-4,12,13]. Less frequent clinical manifestations include breast mass (10–20%) or nodules and lymph node involvement (15%) that are related to a more aggressive disease[4,9,10]. The median age of presentation is 52 years[12] and time between surgery and onset of the symptoms has been estimated to be of 7 to 10 years[3,4]. A seroma that appears a year after breast surgery not associated to trauma or implant infection, should be investigated due to the risk of BIA-ALCL, which is estimated at approximately 10%[2,4]. In our case report, the patient manifested the first symptoms 7 years after breast surgery.

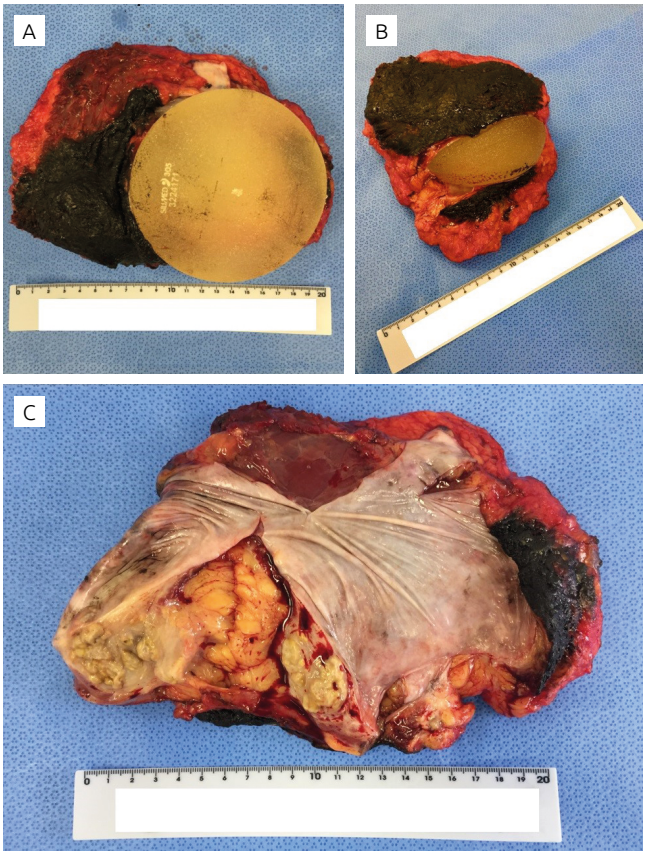

Figure 3. Relationship between breast tissue, capsule implant, deep margins and neoplastic mass. (A, B) Right breast tissue, weighing 725 g and breast implant sizing of 11.5 cm surrounded by a fibrous capsule and deep margin marked with ink. (C) Right breast tissue with heterogenous neoplastic mass in lower inner quadrant, measuring 4.0 × 3.8 × 3.5cm, underlying the implant capsule and adjacent to the deep margin (black ink).

BIA-ALCL is subdivided in two histological groups:

- *in situ* disease characterized by cell proliferation confined to the implant fibrous capsule, clinically presented as a seroma;
- invasive disease characterized by cell proliferation infiltrating the capsule and/or adjacent tissues, often manifested as a breast mass[13].

In addition, *in situ* and invasive BIA-ALCL can coexist; besides, *in situ* disease can advance to invasive form[13].

Diagnosis of BIA-ALCL requires a multidisciplinary approach. Breast ultrasound (US) is the first exam performed to define the extent of the seroma, the presence of capsular masses or regional lymphadenopathy. US is also useful to guide seroma aspiration and for tissue biopsy[5]. Sensitivity and specificity of US for detecting a seroma (84 and 75%) and a mass (46 and 100%) in BIA-ALCL patients is similar or better than computed tomography (CT) or magnetic resonance imaging (MRI)[2]. Breast MRI or PET/CT is indicated for cases with doubtful findings, and to evaluate invasion of chest wall prior to surgical treatment[2]. Pet-scan is also recommended for staging and to investigate the presence of disease out of the breast[2,4]. Pathological analysis of the seroma cytology or core-biopsy of the nodule or mass are necessary for BIA-ALCL diagnosis[2,4].

Literature reveals two staging systems for BIA-ALCL: the Lugano revision of the Ann Arbor Staging System, which stages it as a "liquid tumor"[2,5], and the American Joint Comitte on Cancer (AJCC), which stages it as a "solid tumor", based on tumor, lymph node and metastasis (TNM)[2]. According to the Lugano staging system, stage IE corresponds to disease limited to one breast only and stage IIE to ipsilateral lymph node involvement[17]. As per TNM classification, stage IA corresponds to disease confined to the effusion, stage IB to an early capsular invasion, stage IC to a mass confined to the capsule, stage IIA to a spread external to the capsule, stages II and III to lymph node involvement and stage IV to metastasis(es) to distant sites[2]. BIA-ALCL is often present as an early-stage disease, with 83% of the patients presenting stage IE (Lugano) and 35.6% stage IA, 11.5% stage IB, 13.8% stage IC and 25.3% stage IIA (TNM)[2].

Recommended treatment is capsulectomy, implant removal, excision of the breast mass with free pathological margins and of suspicious lymph nodes[2,4]. Removal of the contralateral implant may be considered since 4.6% of the cases also revealed BIA-ALCL on the contralateral breast[2,9]. It is essential to provide a perspective of future breast reconstruction for patients. We recommend this orientation to be performed prior to the surgical procedure in order to minimize resulting trauma. When performed, further reconstruction should be done with smooth implants[4]. Psychological follow-up is always recommended.

The role of adjuvant therapy remains unknown[4]. There is no standard approach to treatment of patients in cases of incomplete margins, locoregional spread or disseminated disease[4]. Adjuvant chemotherapy was based on treatment of systemic T-cell lymphoma[5] and NCCN guidelines support using anthracycline-based chemotherapy or alternatively, Brentuximab vedotin[2]. Radiotherapy should be considered in the cases of residual, localized or unresectable disease and after local recurrence[4].

BIA-ALCL appears to be an indolent disease with an excellent prognosis when confined to the capsule and treated with complete surgical resection[18]. The overall survival rate estimated by Clemens et al., after analyzing eighty-seven BIA-ALCL patients, was 94 and 91% at 3 and 5 years, respectively, and the 3-year and 5-year event free survival rates were both 49%[9]. Local recurrence rate is related to incomplete surgical excision, which reaffirms surgical importance in the treatment of the disease[4,9].

In Brazil, this is the second case of BIA-ALCL to be reported, and the second LFS-related BIA-ALCL worldwide. Due to the remarkable risk of breast cancer in LFS women, it is still important to discuss indication of risk-reducing mastectomy in female carriers, even if it involves breast implant placement. Because of the possible risk of BIA-ALCL, it is relevant to consider the use of smooth implants or autologous flap in these patients.

CONCLUSION

BIA-ALCL is a rare and newly recognized disease whose pathogenesis is still under research. It should be suspected in patients that manifest chronic seroma associated with the presence of breast implants, even more so if the patient is a carrier of a genetic mutation that enhances the risk of developing malignancies. Diagnosis requires an approach with imaging exams and a biopsy, and all the findings should be discussed by a surgeon, a radiologist and a pathologist together. In cases that any genetic syndromes are involved, when reconstructive surgery will be performed, the use of smooth implants or of an autologous flap is recommended.

Moreover, in clinical practice, it is necessary to focus on patient education, to clarify the rarity of the disease, but that its existence is real and can occur. In addition, knowledge of the disease characteristics allows patients to remain alert to the initial symptoms. Another relevant aspect is the patient's conscious choice to use or not silicone implants, which should always be considered at the time of a surgical indication.

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