

Silicone-induced granuloma of breast implant capsule (SIGBIC): similarities and differences with anaplastic large cell lymphoma (ALCL) and their differential diagnosis

Eduardo de Faria Castro
Fleury¹

Milena Morais Rêgo¹

Luciana Costa Ramalho¹

Veronica Jorge Ayres¹

Rodrigo Oliveira Seleti²

Carlos Alberto Pecci

Ferreira²

Decio Roveda Jr²

¹Radiology Department, IBCC – Instituto Brasileiro de Controle do Câncer, ²Irmandade Santa Casa de Misericórdia de São Paulo, São Paulo, Brazil

Abstract: Primary breast lymphoma is a rare disease and accounts for 0.5% of cases of breast cancer. Most primary breast lymphomas develop from B cells, and the involvement of T cells is rare. Anaplastic large cell lymphoma (ALCL) is a recently discovered T-cell lymphoma associated with breast implants. Only a few cases have been reported to date. It is believed that the incidence of ALCL is increasing because of the increasing number of breast implants. The clinical presentation is variable and can manifest as a palpable mass in the breast or armpit, breast pain, or capsular contracture. Because of the rarity of the disease and the lack of knowledge to date, clinical diagnosis is often delayed, with consequent delays in treatment. The cause and pathogenesis have not been fully elucidated, and there are no evidence-based guidelines for diagnosis, treatment, or follow-up of this disease. We present a review of cases of patients with silicone breast implants, including ALCL, a rare type of breast cancer that is still under study, and silicone-induced granuloma of breast implant capsule and its differential diagnosis, and discuss if a silicone-induced granuloma of breast implant capsule could be the precursor of the disease.

Keywords: lymphoma, granuloma, breast cancer, implant

Introduction

Breast cancer is the most common cancer among women and is considered the leading cause of cancer mortality among women in Brazil. More than 95% of cases of breast cancer are carcinomas. Other malignant tumors may occasionally develop in breast tissues, including sarcomas, secondary metastases, and lymphomas.¹

Primary breast lymphoma

Primary breast lymphomas (PBLs) are rare neoplasms, representing approximately 0.5% of the cases of breast cancers and 2% of the cases of extranodal lymphomas.² PBLs originate from periductal and perilobular lymphoid tissues of the breast and may be related to lymphoid tissues associated with mucous membranes.³ Most PBLs are derived from B cells, and tumors with T-cell phenotypes are rare (less than 6% cases).⁴ The average age at onset of PBL is 57 years.⁵

The clinical and radiological manifestations of PBL are indistinguishable from those of other breast tumors. Therefore, immunohistochemistry is fundamental for the diagnosis of these tumors.⁴

Correspondence: Eduardo de Faria Castro Fleury

Rua Maestro Chiaffarelli, 409, Jardim Paulista – São Paulo 01432-030, Brazil
Tel +55 11 98148 1188

Email edufleury@hotmail.com

These tumors are usually single, painless, and well-defined and have an elastic consistency.

The diagnostic criteria originally defined for PBL continue to serve as the standard definition of the disease,⁶ which include the following:

- An initial site of disease presentation in the breasts;
- The absence of a previous history of lymphoma;
- The absence of disseminated disease at diagnosis;
- An association between the lymphoma and breast tissue on histopathological examination;
- An association between the axillary lymph nodes involvement with breast lymphoma.

Anaplastic large cell lymphoma (ALCL)

Anaplastic large cell lymphoma (ALCL) is a rare subtype of non-Hodgkin lymphoma of T cells; it represents approximately 3% of cases of non-Hodgkin lymphoma.⁷

Most of the described cases (81%) correspond to ALCL and involve the presence of CD30⁺ and the absence of the *ALK* gene.⁸

ALCL CD30⁺ occurs as a result of the activation and abnormal proliferation of T lymphocytes; it may present in cutaneous or systemic forms. The expression of the *ALK* gene allows the classification of ALCL into two subtypes, which help determine prognosis. The morphological and cytological characteristics of ALCL associated with breast

implants are similar to those of systemic ALK-negative ALCL; however, the latter has a poor prognosis, whereas breast implant-associated ALK-negative ALCL is typically an indolent disease with a much better prognosis.⁹

The interest in ALCL has been motivated by reports of cases of PBLs associated with saline and silicone implants. These cases usually involve surgical findings, and the diagnosis before surgery is unknown.¹⁰⁻¹²

The first case of ALCL associated with breast implants was described in 1997 by Keech and Creech.¹³ In 2011, the United States Food and Drug Administration issued a statement confirming 60 cases of ALCL associated with prosthesis.¹⁴ Since then, the number of cases of ALCL has increased, presumably due to the growing number of breast implants and the greater knowledge of the disease pathology.

The reported incidence of ALCL is one case per 500,000 women with breast implants. The age at onset varies between 34 and 59 years, with an average of 46 years. The disease develops within approximately 3–7 years, with a mean of 5 years after mammoplasty.¹¹

ALCL affects the fibrous capsule around the implant, rarely appears as a solid mass and does not involve the breast parenchyma.^{9,15} The initial presentation in most patients includes seroma without spontaneous resolution, capsular contracture, or peri-implant masses⁸ (Figure 1).

The mechanism involved in the development of lymphoma is uncertain,¹¹ and its pathogenesis is currently under

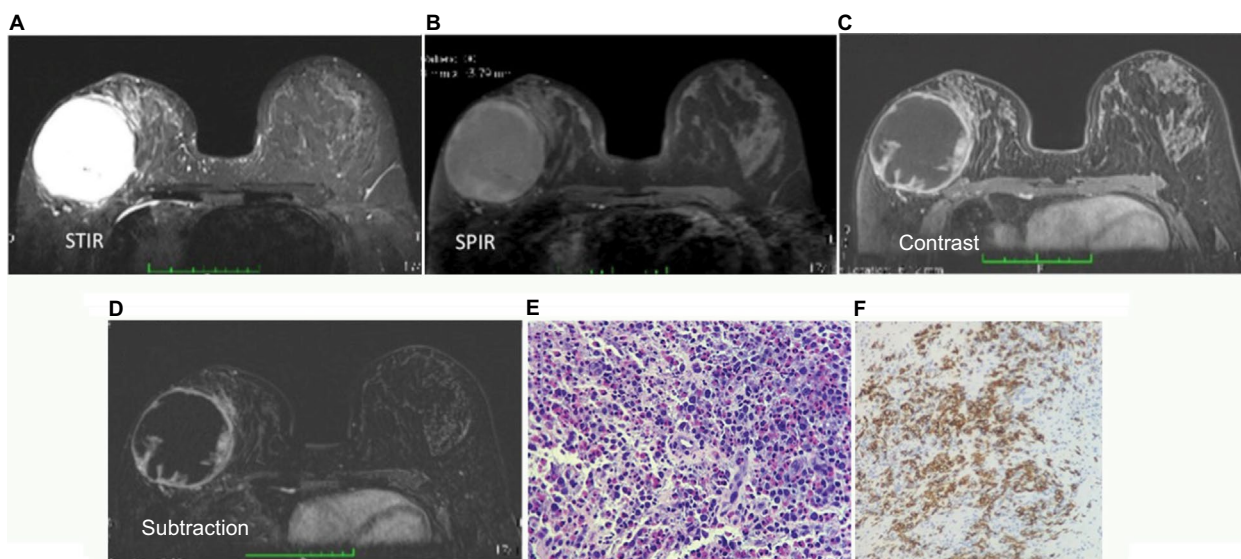


Figure 1 A 57-year-old patient with asymmetric enlargement of the right breast and clinical signs of capsular contracture. **Notes:** MRI images in (A) STIR, (B) SPIR, (C) after the injection of contrast agent, and (D) with subtraction show the heterogeneous tissue in the space between the fibrous capsule and the breast implant associated with fluid fill. These findings are compatible with ALCL. Specimen of core needle biopsy of the lesion shows a proliferation of monoclonal T lymphocytes (E). The immunohistochemistry is positive for CD30⁺ (F). The diagnosis was confirmed as ALCL. Magnification $\times 500$. **Abbreviations:** MRI, magnetic resonance imaging; STIR, short-T1 inversion recovery; SPIR, spectral presaturation with inversion recovery; ALCL, anaplastic large cell lymphoma.

investigation. However, the mechanism may involve an immune response induced by the silicone or polyurethane material in the implant, which may cause an immune over-reaction and induce monoclonal neoplasia with activated T lymphocytes. Other postulated mechanisms involve an indirect reaction mediated by cytokines and toxic damage induced by silicone.¹⁶

Microscopic leakage of silicone from the interior of the prosthesis into the intracapsular area has been described even in cases in which implants are not ruptured. In the case of saline or silicone implants, the capsules may be responsible for chronic local inflammation with T-cell activation and clonal expansion.¹¹

Silicone-induced granuloma of breast implant capsule (SIGBIC)

The SIGBIC is probably a resultant of an autoimmune/inflammatory syndrome induced by silicone (ASIA syndrome). The association between autoimmunity and silicon exposure, similar to that causing the ALCL, may result in the following scenario:

- Silicone leaks from the interior of a normal implant into the intracapsular space;
- Silicon-containing particles are captured by macrophages, resulting in entrapment within lysosomes;
- These macrophages are activated, resulting in the production of cytokines, for example, interleukin-1b, reactive oxygen species, and reactive nitrogen species;
- Apoptosis of macrophages result in the release of silicon-containing particles that can be taken up once again by other macrophages.

Exposure to silicon-containing particles also leads to a massive production of interleukin-17, resulting in an influx of neutrophils that are activated and produce reactive oxygen species and release of myeloid granular enzymes such as myeloperoxidase. Additionally, if there is a capsular disruption, silicon-containing particles are transported to the regional lymph nodes, resulting in a pronounced adjuvant effect. Silica particles induce a type-2 inflammatory response characterized by increase in IgE and IgG1 and chronic activation of T cells, possibly because negative regulators of T cells are dysfunctional in combination with dysfunction of regulatory T cells. It is known that silicones may undergo oxidization to silica and that silicon-containing gel induces an adjuvant effect.¹⁷

Searching the bibliographic databases online on the web, no reference was found to silicone-induced granuloma

in intact breast implants. As seen above, the pathophysiology of ALCL is very similar to that of SIGBIC, where the only difference would be monoclonal neoplasia induced by activation of T lymphocytes. Because they are very rare entities, new studies need to be performed to determine whether ALCL is an evolution of SIGBIC. We also believe that SIGBIC should be underdiagnosed in clinical practice due to its benign course.

Diagnosis

Clinical examination

Clinically, ALCL may present as seroma without spontaneous resolution, capsular contracture, or peri-implant masses,⁸ while SIGBIC may present as a mass. The conditions usually have an indolent course and excellent prognosis, with a good response to excision of the fibrous capsule and removal of the implant. In contrast, cases that involve the presence of masses can be more aggressive and can have poor prognoses.¹⁵

Image diagnosis

The image features of ALCL and SIGBIC will be similar, although ALCL could present as fluid fill within the intracapsular space, while SIGBIC is most often present as an intracapsular mass. It is important to emphasize that the implant should be intact, without signals of visible ruptures by imaging methods.

Mammography is usually the first clinical examination conducted (Figure 2). However, in patients with capsular contracture, their performance may be difficult due to the breast stiffness. Patients must complete a consent form for the examination owing to the risk of rupture by compression of the device.

Ultrasound is the second most common examination and is usually interpreted in conjunction with the mammogram. Ultrasound may be used to guide punctures or biopsies; one

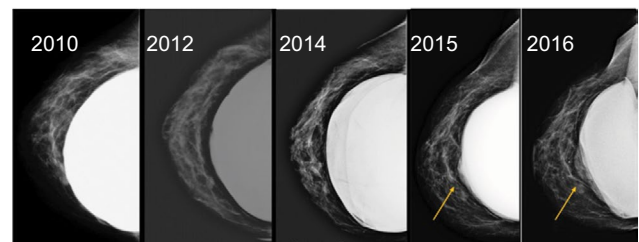


Figure 2 A 53-year-old patient at the breast screening program.

Notes: Sequence of mammography shows a mass developing at the fibrous capsule of the implant in the year of 2015 and subcapsular mass that increase in size in 2016, when compared to 2015 mammogram (arrows). It was given BI-RADS category 4, but she and her physician opted to follow up the lesion. One year later the mass grows up and was given a BI-RADS category 4 again.

Abbreviation: BI-RADS, breast imaging reporting and data system.

of its advantages is its low cost. ALCL findings are often not very specific. Approximately two-thirds of patients present fluid collection around the implant, which is observed in the images, and one-third are characterized by the presence of masses (Figure 3).

Magnetic resonance imaging (MRI) has the best sensitivity for the assessment of suspected cases of lymphoma and evaluation of the integrity of the implant. For these reasons, MRI is widely used in clinical practice (Figure 4).

Cytological/anatomopathological diagnosis

Diagnosis can be made by cytology of the seroma or biopsy of the capsule.⁵ In cases of recurrent seroma that develop approximately 6 months or more after mammoplasty, cytological examination of the aspirate is recommended because the lymphoma cells are found in seroma around the implant,

in the fibrous capsule or within a peri-implant mass.^{8,18} Typically, there is no invasion, other than the fibrous capsule, into the breast parenchyma¹⁸ (Figure 5).

The differential diagnosis between ALCL and SIGBIC is made essentially by the presence of anaplastic monoclonal T cell at optic microscopy, enhanced by CD30⁺ and CD3 immunostain.

Differential diagnosis

No masses should be present in the virtual space between the fibrous capsule and the breast implant. If present, these masses limit the differential diagnosis of ALCL and SIGBIC (Figure 6).

The main differential diagnosis includes the presence of seroma, capsular contracture, late hematoma, and late inflammatory/infectious processes.

Seroma is one of the complications associated with breast implants. It consists of an exudate between the fibrous capsule

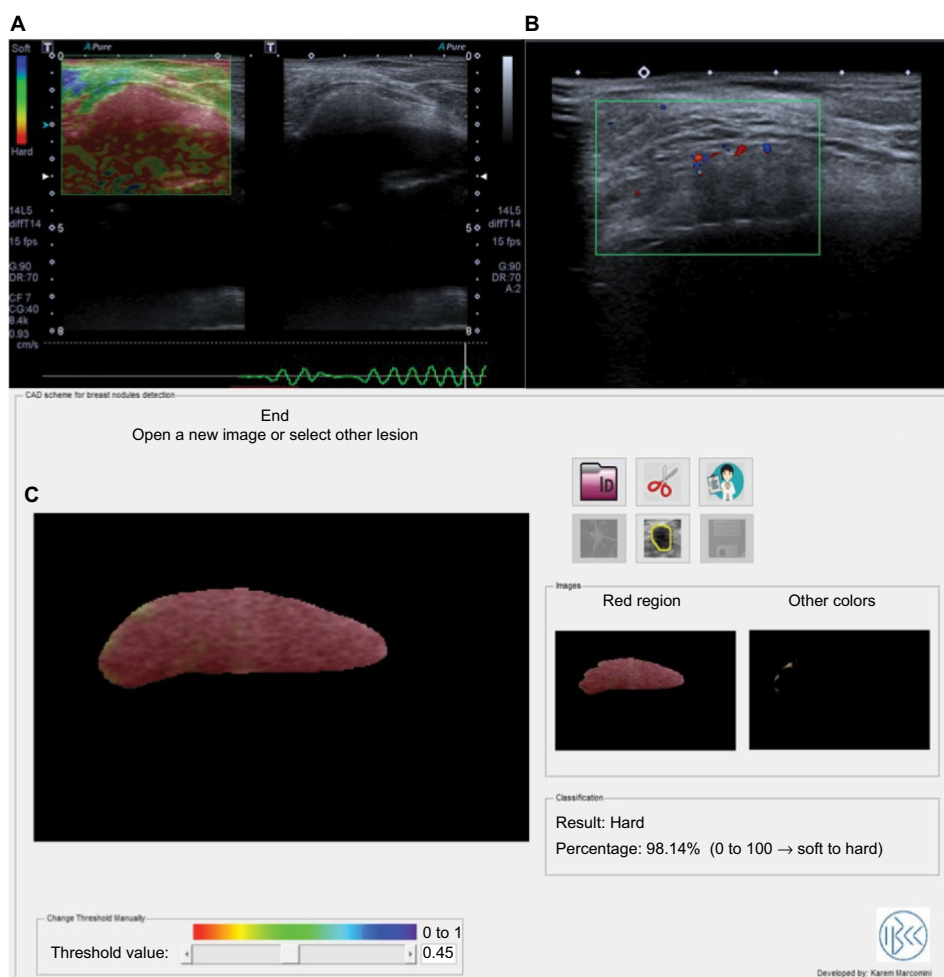


Figure 3 The same 53-year-old patient noted in the earlier figure underwent ultrasound scan that shows (A) a hard mass at the elastography, (B) with high vascularity at the color Doppler scan, and (C) when processing a CAD software of the lesion, the result shows a mass composed essentially of hard tissue, 98.14% of hard tissue. **Abbreviation:** CAD, computer-assisted diagnosis.

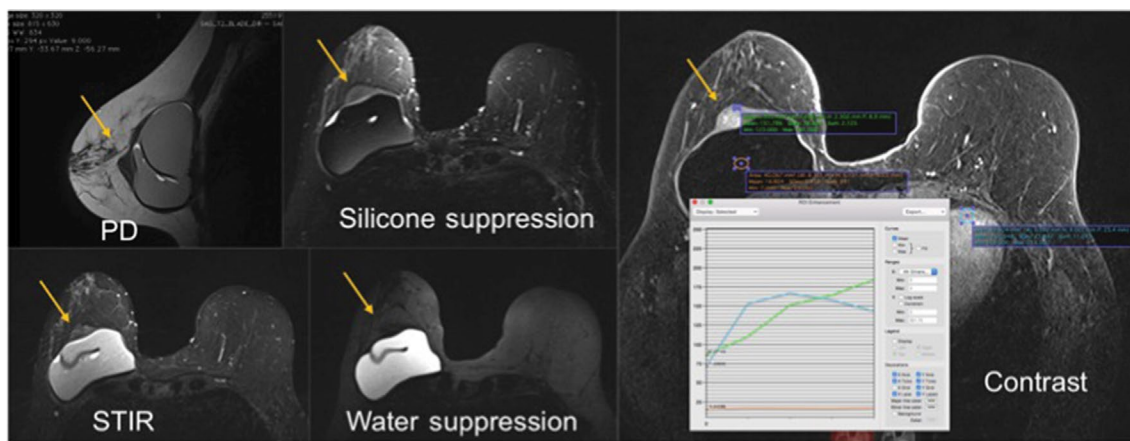


Figure 4 MRI of the same 53-year-old patient noted in the earlier figures.

Notes: A fibrous mass at the same regions of the earlier figures was observed. The characteristics of the signals show a fibrous lesion, with low signal at all sequences and enhancement after the contrast injection. Arrows indicate subcapsular mass with contrast enhancement. There is no signal of implant rupture.

Abbreviations: PD, proton density; STIR, short T1 inversion recovery; MRI, MRI, magnetic resonance imaging.

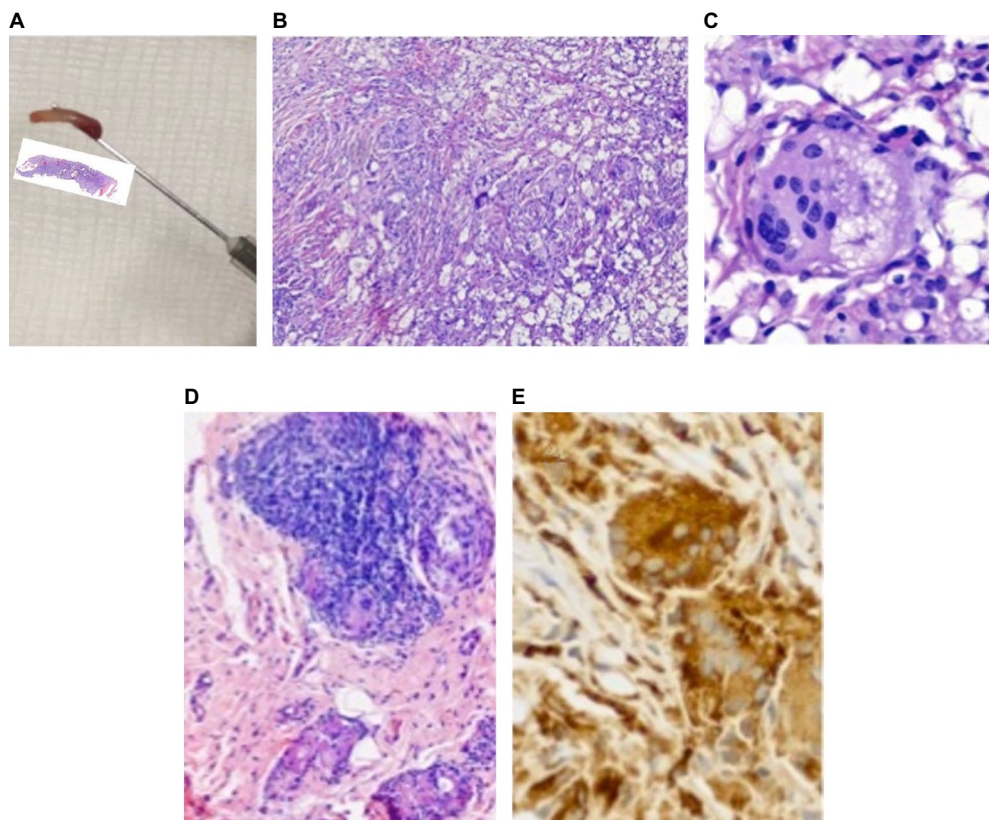


Figure 5 Specimen of core needle biopsy of the lesion shows a rigid lesion.

Notes: The microscopic analysis shows (A) epithelioid granulomatous process with giant cells induced by silicone (B–E). CD68 immunohistochemistry positivity, denoting histiocytic nature of cells. The diagnosis was confirmed as SIGBIC. Magnification for (B) $\times 40$; (C) $\times 500$; (D) $\times 100$; (E) $\times 500$.

Abbreviation: SIGBIC, silicone-induced granuloma of breast implant capsule.

and the implant that is typically reabsorbed spontaneously. The complication is considered late when its clinical manifestation occurs more than 12 months after the procedure. In general, most of the seromas described in the literature are associated with Biocell textured implants, which favor the development of double capsules.¹⁹ Double capsules usually

occur when there is detachment of the fibrous capsule from the surface of the implant, forming a local seroma/hematoma. After resorption, a new, second, capsule is formed.

Capsular contracture results from the proliferation of fibrous scar tissues in the adjacent fibrous capsule; these tissues compress and deform the implant. This complication

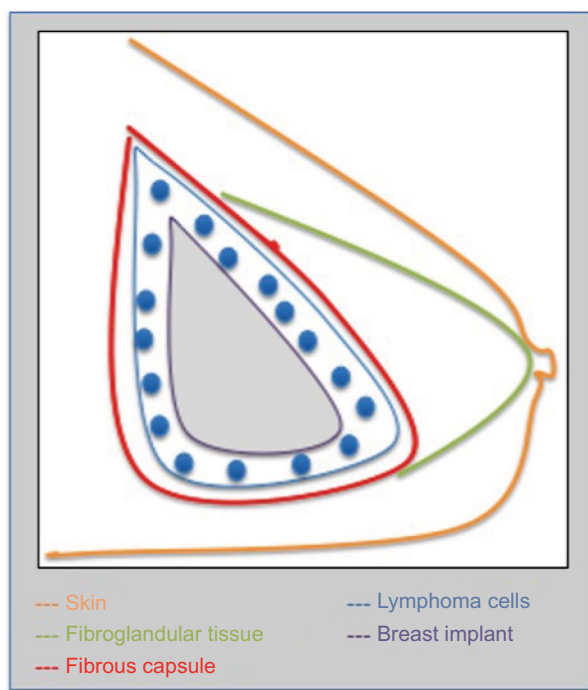


Figure 6 Schematic representation of the location of ALCL and SIGBIC. **Abbreviations:** ALCL, anaplastic large cell lymphoma; SIGBIC, silicone-induced granuloma of breast implant capsule.

may be due to infection, hematoma, or seroma²⁰ (Figure 7). Its clinical scoring follows the classification of Baker and includes the following four grades:

- Grade I: soft breast, with normal visual appearance;
- Grade II: slight stiffening of the breast, with normal visual appearance;
- Grade III: hardening of the breast, with abnormal visual appearance (deformity); and
- Grade IV: hardened breast, with pain and significant visual deformity.

Late hematoma originates from medium-sized arteries located in the implant capsule. Chronic bleeding of these arteries is caused by microfractures in the fibrous capsule. Because of the rigidity of the prosthesis, the retraction of the damaged vessel is limited, which favors new bleeding²¹ (Figure 8).

Late infection can occur after cosmetic surgeries such as breast augmentation, in which 2.9% of patients present infection in the surgical bed; among those affected, 1.7% cases are acute, and 0.8% cases are late. These rates are higher in patients undergoing mastectomy and reconstruction because of the complexity of the procedures and range between 1% and 53%. The onset of late infection may vary from a few months to several years and is different between saline implants (onset within 8 weeks, with an average of 4 weeks) and silicone implants (onset within 24 weeks, with an average

of 8 weeks). Late infections are caused by the colonization of prostheses secondary to blood bacteremia. The microorganisms involved are gram-positive and gram-negative bacteria. Coagulase-negative staphylococci and *Propionibacterium acnes* are the most common strains. The diagnosis is made by liquid culture of the material obtained by fine-needle aspiration, and empirical treatment with vancomycin should be conducted with antibiotics until the results of antibiogram susceptibility testing become available, based on the high number of infections due to β -lactam resistant pathogens, among which are methicillin-resistant *Staphylococcus aureus* and coagulase-negative staphylococci²² (Figure 9).

The main differential diagnoses are not correlated with the presence of masses with anomalous enhancement on MRI. Therefore, the injection of a paramagnetic agent (gadolinium) is essential in MRI examinations of breast implants to determine if the diagnosis of ALCL or SIGBIC should be discarded because of the consequences of late diagnosis. Without the use of contrast media, it is not possible to evaluate the presence of solid masses in the hematoma.

We suppose that SIGBIC is subdiagnosed at the clinical practice due to some factors: lack of information about the implant status at the surgery for the pathologist, and most often the material of capsulotomy is not sent for histological examination. We believe it could be a precursor of the ALCL because both have the same physiopathogeny.

Treatment

The treatment proposed for ALCL and SIGBIC is almost the same: removal of the prosthesis and fibrous capsule. Chemotherapy or adjuvant radiotherapy is not indicated in cases confined to the capsule for ALCL.²³ Despite the poor prognosis of ALK-negative ALCL, the primary cases with silicone implants appear to have an indolent course, with good response to treatment and better disease-free survival.⁸ The reported rate of cure is higher than 90%. Cases with clinical presentation of solid masses are often more aggressive; in such instances, secondary therapy, such as chemotherapy and radiation, is recommended.^{23,24}

Conclusion

Although ALCL and SIGBIC are rare, knowledge about these diseases is essential in patients subjected to diagnostic MRI for the assessment of breast implants because treatment is simple and involves the removal of the prosthesis and the capsule around the prosthesis. Therefore, a contrast agent should be used for the evaluation of breast implants on MRI to ensure that a diagnosis is made before the surgery for

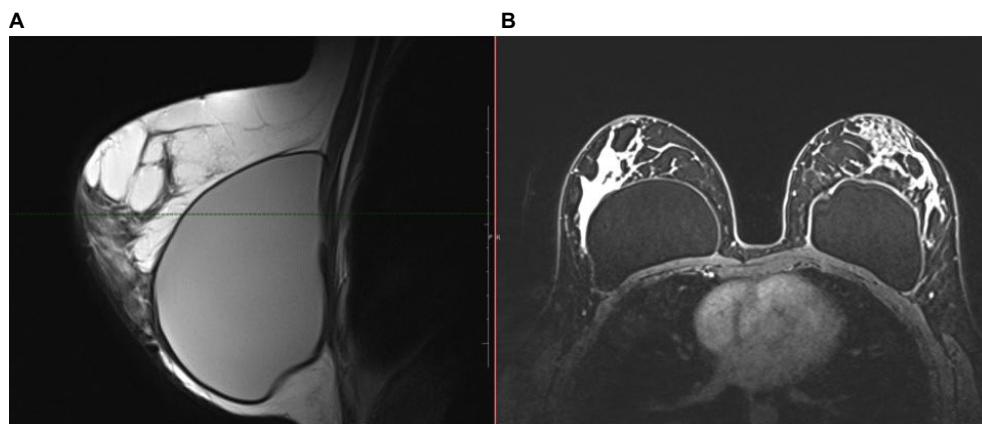


Figure 7 A 43-year-old patient with thickening and discomfort in the left breast.

Notes: (A) Sagittal PD images of the left breast and (B) axial images after injection of the contrast agent show the increase in the anteroposterior diameter of the left breast implant, with thickening of the fibrous capsule and enhanced contrast compared with the right side.

Abbreviation: PD, proton density.

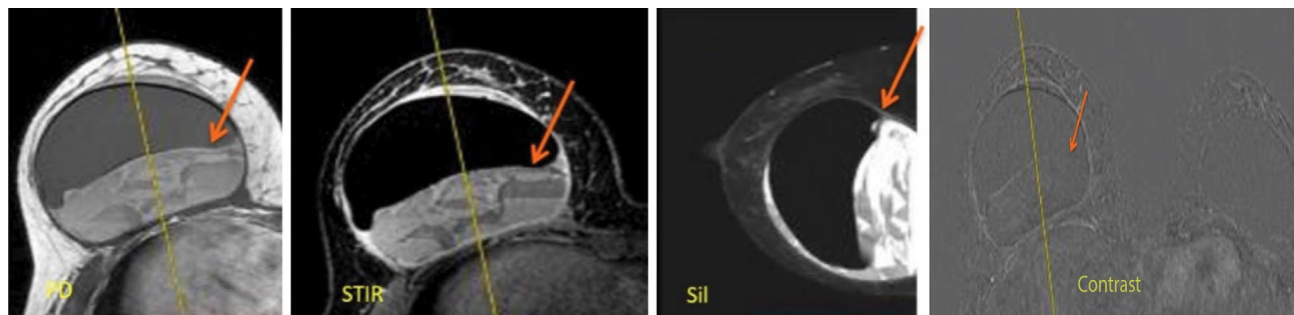


Figure 8 A 48-year-old patient with pain and enlargement on the right breast.

Notes: The MRI shows an intracapsular fluid fill around the implant with heterogeneous, signal compatible with hematoma. There is no mass enhancement after the contrast media injection. Arrows indicate limit between prosthesis and hematoma.

Abbreviations: PD, proton density; STIR, Short T1 inversion recovery; Sil, silicone; MRI, magnetic resonance imaging.

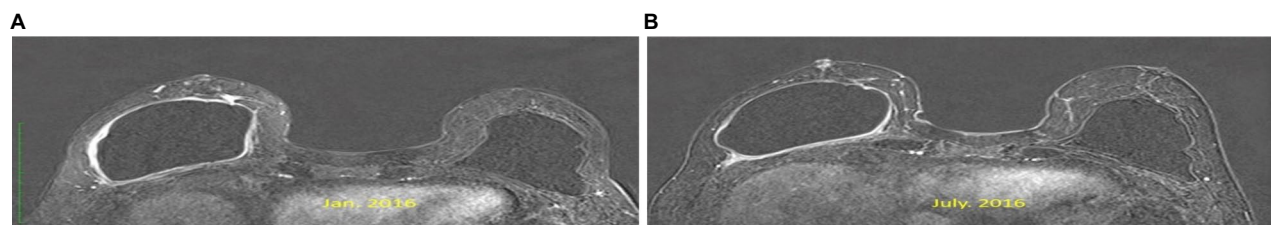


Figure 9 A 35-year-old patient with signs of fluid collection in the right breast 7 years after implantation.

Notes: The image was acquired in January 2016 and shows (A) the diffuse thickening of the fibrous capsule, with contrast enhancement in the adjacent fibrous glandular tissue. The patient was subjected to percutaneous biopsy and was diagnosed with mastitis. Antibiotic treatment was performed and resulted in clinical improvement. An MRI image shows (B) the control of the disease at 6 months and improvement of the image status.

Abbreviation: MRI, magnetic resonance imaging.

prosthesis replacement is performed because of the complications reported for ALCL.

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Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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