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ORIGINAL ARTICLE

Anaplastic large-cell periprosthetic lymphoma of the breast: could fibrin be an early radiological indicator of the presence of disease?

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Summary

Purpose: *The onset characteristics of the anaplastic large cell lymphoma (BI-ALCL) are non-specific and the diagnosis is often difficult and based on clinical suspicion and cytological sampling. The presence of non-pathognomonic radiological signs may delay the diagnosis of BI-ALCL, influencing patient prognosis. This could have an important social impact, considering that the incidence of BI-ALCL correlates with the number of prosthetic implants, which is in constant increase worldwide. The aim of this study was to verify if fibrin can represent a potentially early radiological sign of the disease.*

Methods: *In this study, we present two cases of our series and review the previous studies already described in the literature, searching for any early radiological sign of the disease and reporting a diagnostic work-up process for an early diagnosis.*

Results: *Signs clearly recognizable only of magnetic resonance imaging (MRI) were the following: thickening and hyperemia of the fibrous capsule with seroma and amorphous material (fibrin) present in 8 out of 10 cases (80%), detected on MRI (certain or doubtful).*

Conclusion: *The presence of fibrin in the periprosthetic effusion, well detectable by MRI, could represent an early pathognomonic sign of the disease.*

Key words: *breast implant, periprosthetic anaplastic lymphoma, anaplastic large-cell lymphoma, breast magnetic resonance imaging*

Introduction

Primary breast lymphoma is a rare disease comprising 0.04-0.5% of all malignant tumours, 1-2% of extranodal lymphomas and less than 1% of all non-Hodgkin lymphomas [1,2].

The first case of anaplastic large-cell periprosthetic lymphoma (BI-ALCL) described in the literature was published by Keech in 1997 [3]. In 2011, the US Food and Drug Administration (FDA) issued a communication, updated in 2016, which indicated a small but increased risk of developing a type of T-cell lymphoma in women with prosthetic implants [4].

The progressive increase in prosthetic implants worldwide, and the unspecific symptomatology of

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the disease have led to an increasing interest in detecting the disease in the early stages.

Some studies report an annual incidence of 1 woman in 500,000 prosthesis carriers (1 in 50,000 women over 10 years) [5,6]. However, in 2017 [4] the difficulty of correctly defining incidence and prevalence in rare and only recently known clinical entities is emphasized: many patients, in fact, present an asymptomatic or nonspecific disease that remains unrecognized or otherwise diagnosed only at death, which would suggest an underestimation of BI-ALCL cases compared to official data.

Other works have highlighted a triggering mechanism for cancer cell degeneration in chronic inflammatory conditions [7-9]. There are no significant changes in the incidence of the disease in relation to the type of implant (silicone, saline, hydrogel), the reason for the surgery (aesthetic, reconstructive) and the position (submuscular, subglandular) while an increase in incidence in texturized implants was highlighted [4,6-9]. The disease can occur in a localized form confined to the capsular space in about 2/3 of the cases or, more infrequently, in an infiltrating form [5,7,10].

The localized form is characterized by the presence of dense periprosthetic effusion with pathological cellular clones, no evidence of palpable mass and an excellent prognosis following capsulectomy.

The infiltrating form, which is shown as a palpable mass with or without affected lymph nodes, is much more aggressive, requires chemotherapy and radiotherapy associated with surgery and leads to death in 40% of cases within two years.

The mammogram highlights the periprosthetic effusion as a "double contour" [8,11], showing 73% sensitivity and 50% specificity in detecting abnormalities, but is unable to distinguish between effusion and mass [10]. Ultrasound (US) shows sensitivity/specificity for effusion and detection rate for masses of 75-84% and 46% respectively and MRI 33-82% and 50% [10]. Other and better evaluations

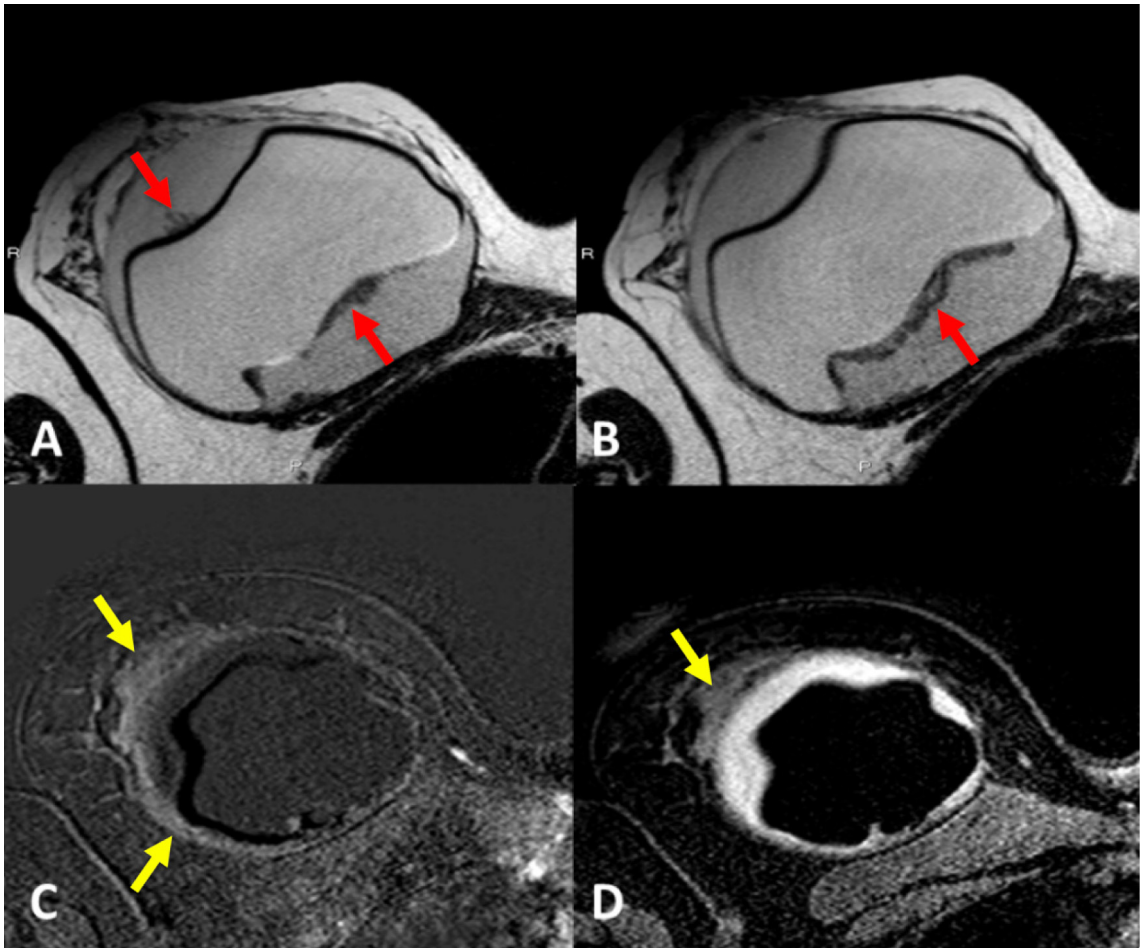

Figure 1. Case #1. MRI images: T2 sequences **(A,B)**; subtracted T1 sequence after contrast material injection **(C)**; T1 sequence after contrast material injection **(D)**. Notice wide seroma between capsule and prosthesis: **(A,B)** amorphous material due to fibrin is appreciable on the inner surface of the fibrous capsule and on the outer surface of the prosthesis (red arrows); **(C,D)** the fibrous capsule appears thickened and hyperemic, especially in the anterior and lateral sectors (yellow arrows).

could derive from the analysis of mammographic and MRI images by radiomics [12-14].

At pathological examination, one of the most frequent findings consists in abundant inflammatory exudate within the periprosthetic effusion and on the inner surface of the capsule, granulation and haemorrhagic tissue, cell necrosis and fibrin together with the cellular clones of the disease [2].

Cellular necrosis, fibrin and haemoglobin degradation products, if present in macroaggregates, are visible on US and especially in breast MRI. Complete remission after capsulectomy is reported in 93% of patients with the disease confined to the fibrous capsule, compared to 72% with the infiltrating mass adjacent to the implant [6].

The aim of this paper study was to verify, through analysis of two new cases of BI-ALCL and a retrospective review of literature, whether degradation products, such as fibrin, may represent potential early radiological signs of the disease.

Methods

We examined the diagnostic pathway in two recent cases of BI-ALCL, focusing on the analysis of common radiological findings and new visible signs. Then, we reviewed the literature on BI-ALCL in order to verify other authors' hypotheses by correlating the radiological signs with the reported pathological anatomy.

Imaging techniques used were Mammography (MX), US and breast MRI: the radiological images were

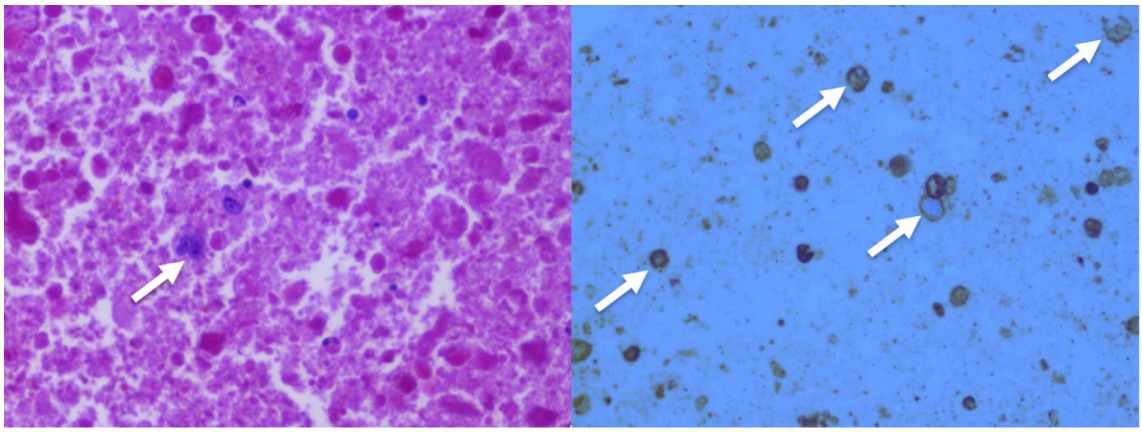

Figure 2. The cytologic analysis of the effusion deposits showed (left) ample acidophilous necrotic amorphous material incorporating large atypical lymphoid cell and histiocytes (white arrow), and (right) a rare large atypical cell with irregularity and CD30 immunoreactivity in the nucleus (white arrows).

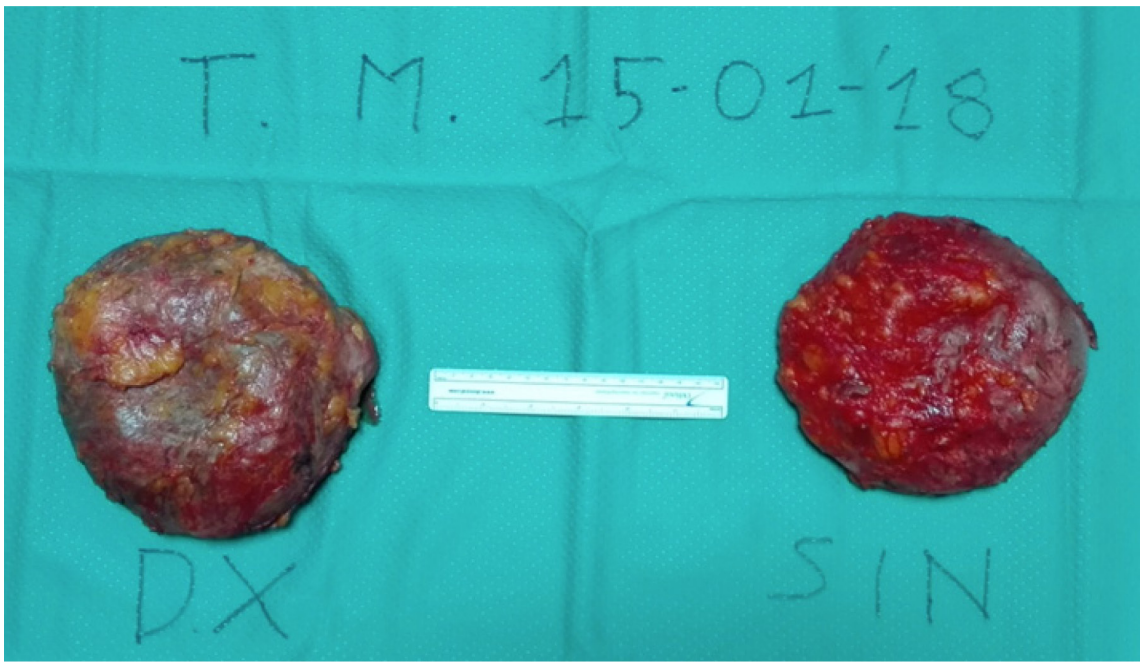

Figure 3. External view after total capsulectomy with the interior prosthesis.

examined by three radiologists with experience in breast diagnostics and the concordant results were reported.

Clinical case #1

A 53-year-old woman underwent bilateral breast augmentation for aesthetic purposes in 2007. In the last 2 years, a breast asymmetry due to evident swelling of the right breast occurred. US and MRI confirmed a large amount of liquid between the prosthesis and the capsule, with a thickening up to 5 cm on the right side. The capsule also appeared irregular and hyperemic in the supra-anterior portions with evidence of multiple aggregation of amorphous, non-vascularized material attached to the prosthesis, due to necrosis and fibrin deposits (Figure 1). The cytological analysis of the effusion deposits showed ample acidophilous necrotic amorphous material incorporating lymphocytes and foamy histiocytes and rare large atypical cells with irregular nuclei and CD30 immunoreactivity referring to the diagnosis of BI-ALCL (Figure 2). The implants (textured 600-cc silicone gel implants placed in the subglandular plane) were removed "en bloc" with total capsulectomy.

Surgery was carried out giving prime importance to the preservation of the vascular supply to the gland, by way of perforating the vessels system [15,16]. During the surgical procedure, the right capsule appeared harder and thicker than the left one, and was firmly adherent to both the inner surface of the gland and the fascia of the pectoralis major muscle. The right capsule appeared less vascularised, thicker and larger due to the major quantity of fluid contained, while the left one was thinner with less fluid inside, and normal surrounding tissue (Figure 3). After fluid aspiration, the capsules were opened, freed from the prostheses, fixed in formalin and sent for pathology: macroscopically it was noticed the density and dark-brown colour of the fluid and the abnormal appearance of the inner surface of the right capsule.

On histopathological analysis, the malignant cells were confined to the intracapsular fluid, and an internal layer of fibrinous tissue adhering to the inner surface of the capsule with abundant necrotic debris was found. The patient underwent only capsulectomy and implant removal and was disease-free at the time of the last follow-up in December 2018.

Clinical case #2

A 27-year-old woman, who underwent a subglandular bilateral augmentation mammoplasty 10 months earlier, came to our attention with a painful left-sided symptomatology associated with ipsilateral lump in the

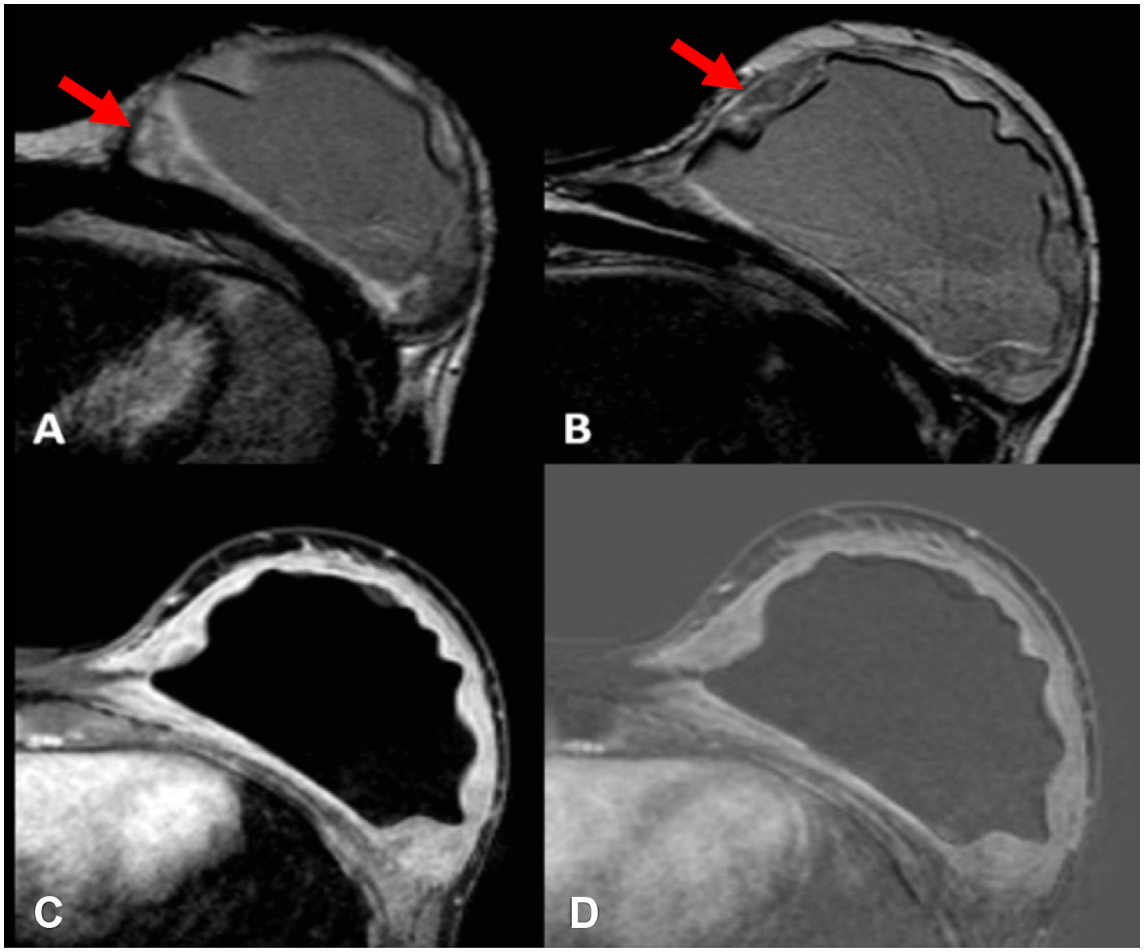

Figure 4. Case #2. MRI images: T2 sequences **(A, B)**; T1 sequence after contrast material injection **(C)**; subtracted T1 sequence after contrast material injection **(D)**. Notice diffuse thickening of both the fibrous capsule and the hypointense amorphous material in all sequences along the outer margins of the left prosthesis caused by fibrin deposits (arrows).

left axilla. US showed corpusculated periprosthetic fluid and enlarged lymph nodes in the left axilla. As in the previous case, the patient underwent MRI examination.

The right implant appeared regular with no significant alterations. On the left side, there was a large subcapsular fluid effusion of up to 3 cm in diameter with hypervascular inhomogeneous tissue, concentrically placed around the implant, with a maximum thickness of 2 cm. There was an evident diffused thickening of both the fibrous capsule and a hypointense amorphous material in all the sequences along the outer margins of the left prosthesis attributable to fibrin deposits was detected (Figure 4). In the left axilla, enlarged lymph nodes were found, with inhomogeneous signal intensity and a maximum diameter of 2 cm.

Cytological examination of the subcapsular fluid and microhistological sample of the tissue confirmed the diagnosis of BI-ALCL.

Results

In both cases, the fibrous capsule showed signs of thickening and hyperaemia with extensive effusion between the capsule and breast implant and the presence of amorphous material adhering to the inner surface of the capsule, due to necrosis and fibrin deposits, as confirmed by post-surgical histopathological examination. Both these signs were clearly recognizable on MRI alone.

The possible presence of amorphous material caused by fibrin deposits has been retrospectively highlighted in 8 out of 10 cases (80%) detected on MRI images (certain or doubts): two cases without evidence of fibrin related to advanced disease.

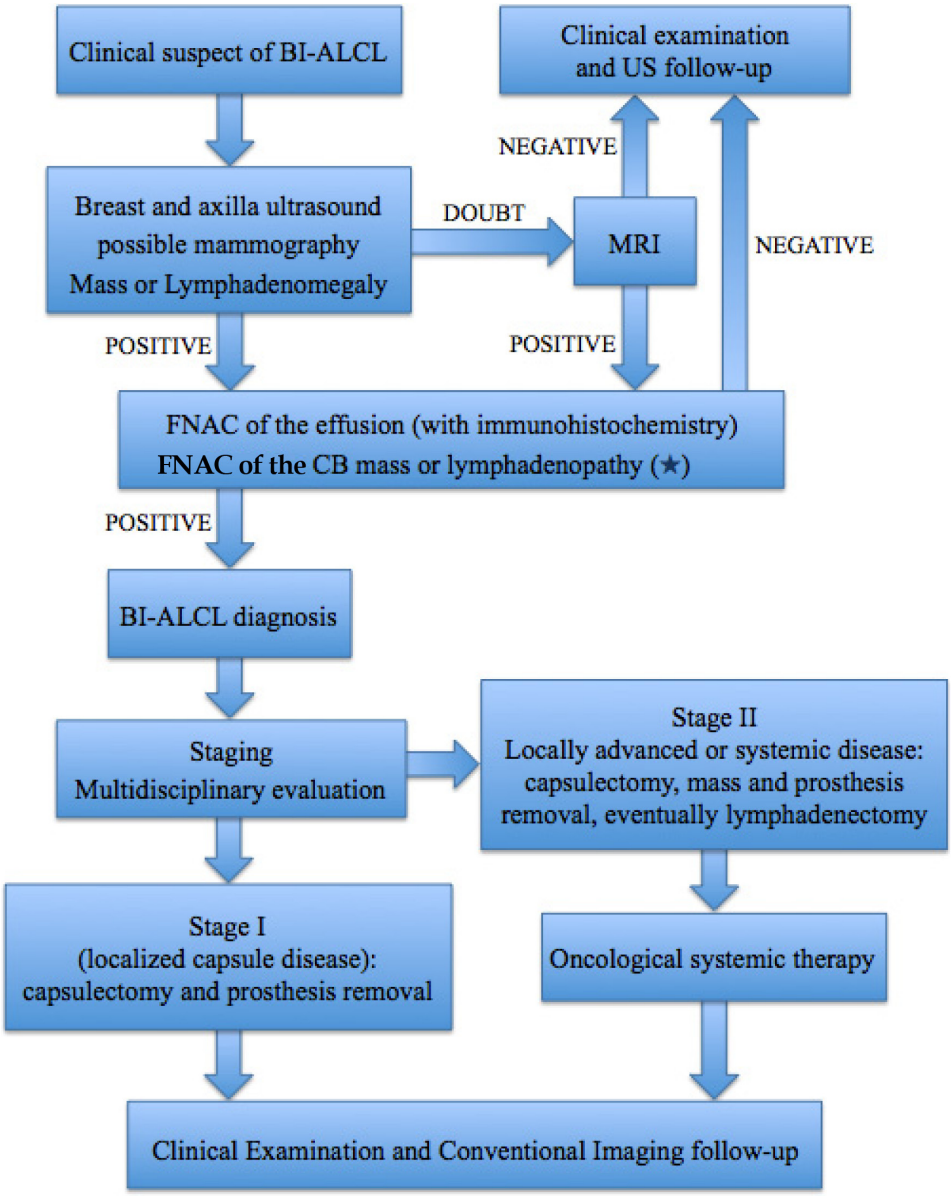

Figure 5. Flow chart showing the current management of BI-ALCL. CB stands for core biopsy. The asterisk represents the starting point of the common path between the current management of BI-ALCL and the alternative one (Figure 6).

Discussion

Many cases of BI-ALCL reported in the literature have recently been associated with texturized breast implants and a state of chronic inflammation due to silent fibrous capsular infections with a malignant transformation of T lymphocytes [1,5,7-9,17,18]. BI-ALCL occurs more frequently as a periprosthetic seroma in which the tumour cells are confined and sometimes as a solid mass infiltrating the periprosthetic capsular wall and the surrounding connective tissue [6,19]. It has been suggested that these findings represent different stages of a single disease rather than two distinct clinicopathological variants and that the periprosthetic seroma constitutes the initial stage and, therefore, requires different treatment [19,20]. Indeed, the removal of the implant and a total capsulectomy are indicated in the non-invasive variants.

BI-ALCL signs are mostly not pathognomonic and this is a major limitation leading to misunderstanding or delaying the diagnosis.

The reduced number of purely radiological diagnoses and the absence of specific signs could also be linked to the lack of knowledge and experience, as in the case of other rare diseases.

The cytological evaluation of the serum carried out on material taken using the fine-needle aspiration cytology (FNAC) method emerges as the gold standard for a precise diagnosis of BI-ALCL, together with the expertise of dedicated pathologists. Indeed, the periprosthetic seroma may be the early manifestation of a BI-ALCL and its cytological examination must be integrated into the diagnostic algorithm for a timely diagnosis.

Consequently, current management of the disease is mainly based on clinical and cytological diagnosis as schematically shown in Figure 5, but the role of imaging in early diagnosis could increase in the presence of more specific signs. For this reason, the MRI could be used not only for the diagnosis of possible pathologies, but also for monitoring them once they have been diagnosed. We can hypothesize a greater incidence in the population of women with prostheses than that reported in literature.

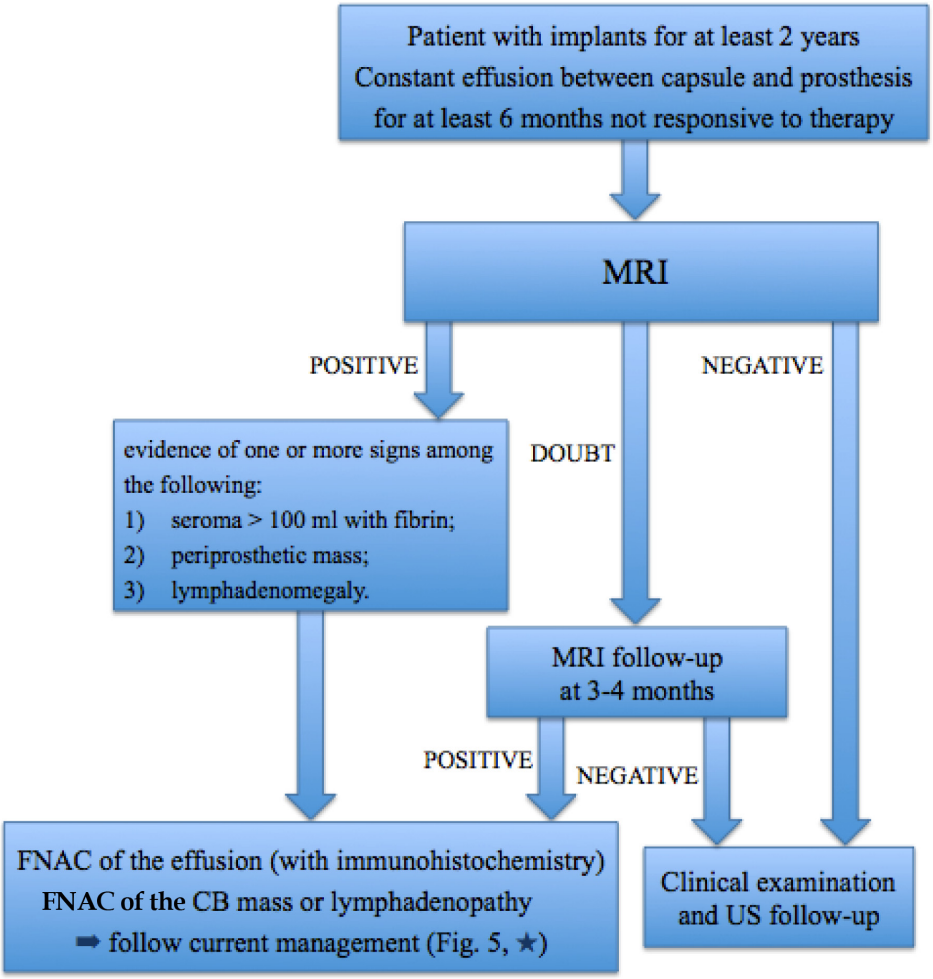

Figure 6. Flow chart showing a proposal for the alternative management of BI-ALCL. The asterisk represents the point from which starts the common path with the current management of BI-ALCL shown in Figure 5.

Table 1. BIA-ALCL case reports in literature. Analysis of MRI images

First author	*Age, years*	*Reason of implant*	*Age of implants (years)*	*Clinical symptoms*	*Radiological signs*	*MRI sequence type*	*Number of images*	*Visible amorphous material*
Fleury [1], 2017	48	unknown	unknown	Pain and enlargement of right breast	Heterogeneous effusion	STIR, SPIR, GE T1 with contrast agent and subtraction	4	YES
Kaartinen [5], 2017	unknown	unknown	unknown	unknown	Inhomogeneous effusion with no mass in left breast	T1 Fat sat	1	IN DOUBT
Xu [7], 2014	68	reconstructive	6	Left breast mass	Effusion, mass with infiltration of capsule and chest wall	T1 pre-contrast T2 Fat sat	2	YES
Hart [8], 2014	31	cosmetic	16	Enlargement of right breast	Effusion in right breast, partial inhomogeneous signal (unclear images)	T2	1	IN DOUBT
Berlin [9], 2018	58	cosmetic	2	Swelling of right breast	Effusion + mass + lymphadenopathy	T2 Fat sat	2	NO
Eisenberg [11], 2018	57	cosmetic	2.5	Swelling, enlargement, palpable mass of right breast	Homogeneous effusion, pericapsular mass, lymphadenopathy	T1, T1 Fat sat with contrast agent, T2	4	NO
Park [17], 2014	62	cosmetic	4	Swelling of left breast	Intracapsular rupture of the prosthesis effusion, focal posterior thickening of the prosthesis (minimal amorphous material adherence)	T2	1	YES
Letter [18], 2016	32	cosmetic	16	Pain, swelling of right breast	Periprosthetic effusion with minimal posterior right breast amorphous material	T2	1	YES
La Forgia, 2018 (CASE #1)	53	cosmetic	10	Swelling and right breast deformity	Periprosthetic effusion with abundant amorphous material	TSE-T2, STIR, T1 with contrast agent and subtraction	4	YES
La Forgia, 2018 (CASE #2)	27	cosmetic	1	Swelling of left breast	Periprosthetic effusion	TSE-T2, STIR, T1 with contrast agent and subtraction	4	YES

The signs of haemoglobin degradation products are clearly visible in ultrasound and especially in breast MRI: the latter is able to differentiate, by means of the paramagnetic contrast medium, between the amorphous material and the active neoplastic tissue.

Since seroma is the most frequent, isolated but also non-specific manifestation of the initial disease, its constant evidence, in association with the presence of fibrin and periprosthetic necrosis detected during an MRI investigation, and in the absence of trauma, could be an early indicator of the disease and could permit a targeted cytological examination.

Moreover, as verified in our experience, these degradation products make the effusion turbid and corpuscular in the US, allowing an initial differential diagnosis between the simple and the neoplastic seroma.

We carried out a review of literature, retrospectively evaluating the cases of BI-ALCL with periprosthetic effusion that reported at least one MRI image: three radiologists with great experience in breast MRI verified the images reported in the published articles.

Periprosthetic/pericapsular amorphous material was visible in 6 out of 10 cases, while 2 cases appeared doubtful or discordant. In the remaining two cases the amorphous material was not visible but its absence did not exclude the possibility of its presence in other images of the same examination not presented in the article. A summary of the data is reported in Table 1.

In our experience, the presence of easily recognizable amorphous material made up of necrosis and fibrin deposits within a chronic pericapsular effusion could suggest BI-ALCL in a very high percentage of cases ranging from 60 to 80%.

This data, if confirmed in a more conspicuous number of studies, could suggest an alternative screening pathway (Figure 6) using breast MRI in women who have had chronic periprosthetic effusion for at least 6 months. The presence of fibrin and visible necrotic material would indicate immediate cytological sampling and the suspected pathological diagnosis with a better probability of identifying a greater number of cases.

Conclusion

The BI-ALCL of the breast represents a pathological condition associated with prosthetic implants, with good prognosis if recognized in the initial stage. Diagnostic imaging, and in particular breast MRI, plays an essential role in this pathology as it allows to detect periprosthetic corpuscular effusion, hypervascularized periprosthetic tissue and axillary lymphadenopathy. The presence of fibrin in the context of periprosthetic effusion, which is easily detected by MRI, could represent an early pathognomonic sign of the disease to be searched for in all cases of suspected periprosthetic effusion, thus leading to an easier diagnosis of the disease.

Conflict of interests

The authors declare no conflict of interests.

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