Management of extended breast implant-associated anaplastic large cell lymphoma

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SUMMARY

We report the case of a 69-year-old woman who presented an aggressive breast implant-associated anaplastic large cell lymphoma with supra- and infradiaphragmatic disease. The diagnosis was made 17 years after her first prosthesis, following a right breast carcinoma, and three years after the replacement of this first prosthesis. Breast implant-associated anaplastic large cell lymphoma is a rare form of non-Hodgkin lymphoma caused by a breast implant. Unique features of this case include the fast clinical extension of a lymphoma that is indolent in the vast majority of the cases. Indeed, less than two months after the first symptoms on the breast, cutaneous metastasis appeared on the right arm. The key diagnosis exams are histology and immunohistochemistry including CD30 and cytotoxic markers and a PET-scan to evaluate the extension of the disease. The treatment should include removal of the prosthesis and any associated mass. Local residual or unresectable disease may benefit from radiation therapy to the chest wall. For regional lymph node involvement or confirmed extended disease, adjuvant chemotherapy more in line with systemic anaplastic large cell lymphoma anaplastic lymphoma kinase-negative treatments is recommended. Finally, brentuximab vedotin, an anti-CD30 monoclonal antibody, showed encouraging results in refractory disease but still needs more prospective trials.

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INTRODUCTION

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is an extremely rare form of non-Hodgkin lymphoma recently recognised as a provisional entity classified in the group of peripheral T-cell lymphomas to which anaplastic large cell lymphoma (ALCL) belongs. BIA-ALCL is one of the four distinct forms of ALCL.[1]

Among women with breast implants, the absolute risk of developing BIA-ALCL is extremely low but significantly higher than that of primary ALCL of the breast in the general population. This was illustrated by a Dutch study on approximately nine million women that reported an 18-fold higher rate of ALCL arising in the breast among women with breast implants compared with women who did not have implants.[2]

The median delay between a breast implant and neoplasia is usually ten years but can occur after one year or more than 32 years.[3]

Some studies have been conducted to explain the pathogenesis and risk factors of BIA-ALCL that can appear for either cosmetic or reconstructive indications.[4] One of them explained the implication of chronic T-cell stimulation against the prosthetic material, with local antigenic drive, leading to genetic degeneration, dysplasia and ultimately to lymphoma.[5] Another study compared capsules of textured and smooth implants in pigs and showed that there are increased lymphocytes on textured breast implants, with a T-cell predominance.[6] Therefore, in 2016, the French Agence Nationale de Sécurité du Médicament (ANSM) forced breast implant manufacturers to submit clear safety sheets for textured

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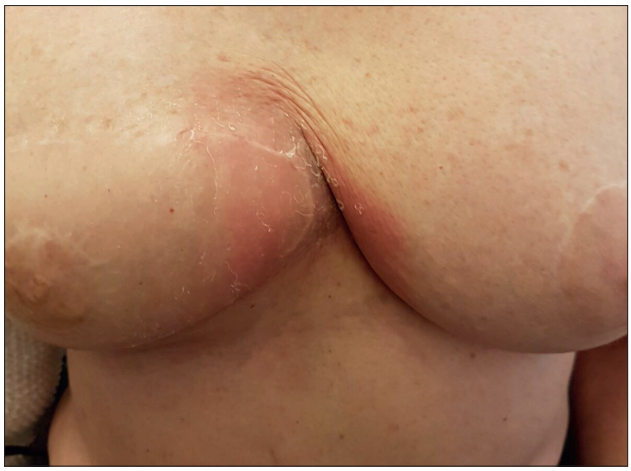

FIGURE 1. Redness on the internal side of the right breast, on intermammary and the inferomedial quadrant of the left breast.

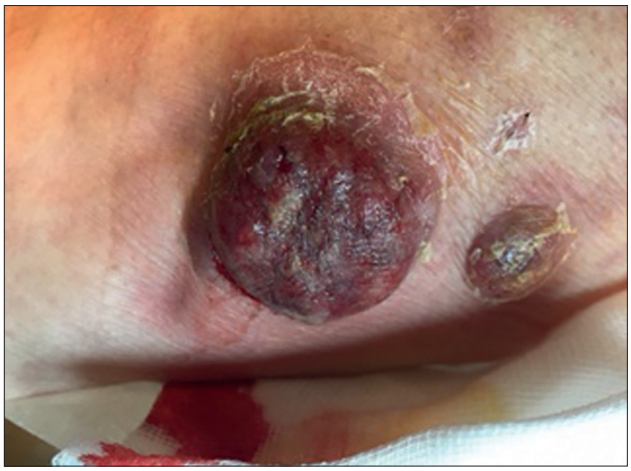

FIGURE 2. Oozing nodules on the right arm.

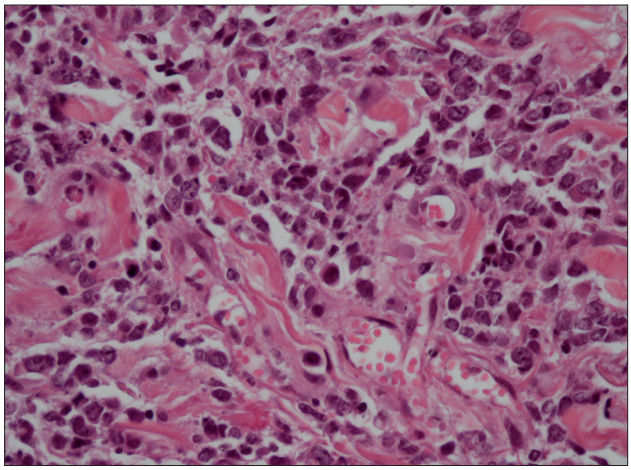

FIGURE 3. The sample was diffusely infiltrated by anaplastic cells with eosinophilic cytoplasm. The nucleus contained one or more large nucleoli (haematoxylin-eosin, original magnification x400).

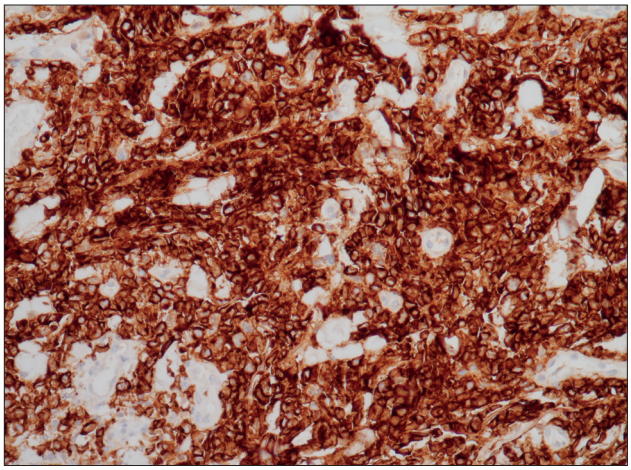

FIGURE 4. At immunohistochemistry, the atypical cells were strongly positive for CD30 (CD30 immunoperoxydase, original magnification x200).

implants.[3] The study by Hu *et al.*, compared the implant capsules between patients with BIA-ALCL and patients with normal capsular contracture. They underscored a high bacterial count and the predominance of a gram-negative bacteria *Ralstonia pickettii* in BIA-ALCL patients, which is a common contaminant of drinking water and soils.[7] This study confirms the evidence that standard care of sterility like antibiotic prophylaxis and no-touch practice must be respected by every centre involved in breast implant surgery and that further research is required for the identification of risk factors and prevention of future cases.

BIA-ALCL is fortunately a highly curable disease because most cases are following an indolent course and can be managed by surgery alone.[8]

Our case is the fifth reported of BIA-ALCL in Belgium (according to the Federal Agency for Medicines and Health Products). According to the incidence in surrounding countries, this is probably not reflecting the real incidence in Belgium, but the low rate of declaration to health authorities.[9] Moreover, our patient's lymphoma has been diagnosed at an uncommon disseminated stage (10-35%). This allows us to review the management from diagnosis to treatment.

CASE REPORT

A 69-year-old woman consulted for swelling of the right breast and indurated redness that appeared first on the internal part of her right breast extending progressively to the intermammary site and the inferomedial quadrant of the left breast (*Figure 1*).

Less than three weeks later, large and necrotic unpainful

subcutaneous metastatic nodules occurred on the right arm (*Figure 2*).

The performance status remains good (ECOG was valuated at 1). On physical examination, there was neither adenopathy nor liver-splenomegaly.

ONCOLOGICAL HISTORY

- 1989: Right invasive breast ductal carcinoma (grade II) with axillary lymph nodes extension. The treatment consisted of a right breast mastectomy followed by chemotherapy (eight cycles of CNF: cyclophosphamide, novantrone and 5-fluorouracil), radiotherapy and hormonal therapy.
- 1990: placement of right prosthesis and reduction of the left breast (no information about the implant type).
- 2014: replacement of the right prosthesis and placement of a prosthesis on the left breast (no information about the implants type)

COMPLEMENTARY EXAMS

Ultrasound (US) showed peri-prosthetic liquid and a hypoechoic heterogeneous nodule, slightly vascularised. The fine-needle aspiration of this liquid showed the presence of naked nuclei and lymphocytes.

To establish diagnosis, biopsies of the peri-prosthesis tumour mass and of the nodule on the right arm were performed. These biopsies showed fibrous and muscular tissues diffusely infiltrated by large cells.

The neoplastic cells were with moderately abundant eosinophilic cytoplasm, with central nucleus, pleomorphic, often with little nucleolus (*Figure 3*).

At immunohistochemistry, these large cells were strongly positive for CD30 and cytotoxic markers, had a weak expression of CD4 and CD8 and were negative for CD20 and for the other markers (*Figure 4*). The Ki 67 index was very high (100%). Fluorescence in situ hybridisation did not show translocation of the anaplastic lymphoma kinase (ALK) gene in 2p23 nor *DUSP22/IRF4* translocation.

The presence of a monoclonal T-cell rearrangement was demonstrated by polymerase chain reaction.

Finally, disease extension was assessed using a positron emission tomography scanner (PET-CT scan) showing that the mammary right tumour extended to the right arm, with also digestive and inferior left leg metastases (*Figure 5*). The bone marrow biopsy was negative and clinical staging according to Ann Arbor classification (*Table 1*) corresponded to a stage IV.

TREATMENTS

After informed consent, the patient was included in the protocol romidepsin-CHOP (Ro-CHOP, EUDRACT: 2012-001580-68) corresponding to a phase III, randomised, prospective, multicentric study evaluating the benefit of the addition of romidepsin to a standard CHOP (cyclophosphamide, doxorubicine, vincristine and prednisone every three weeks) regimen to patients with histologically proven T-cell lymphoma.[10] Romidepsin is a histone deacetylase inhibitor targeting the epigenetic regulation of cancer.[11]

The patient was included and randomised in the standard CHOP arm and received six cycles every 21 days.

She was in complete remission after this treatment and a bilateral breast implant removal surgery was performed. Chemotherapy was performed first because of the aggressive course of the disease and patient preference.

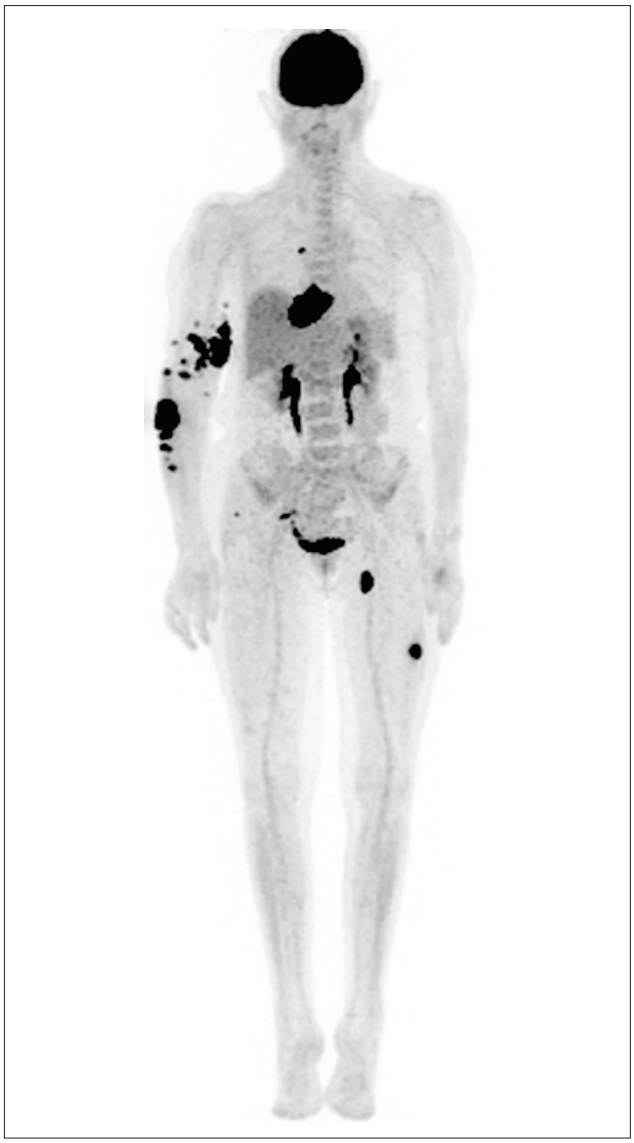

FIGURE 5. Maximal intensity projection view (MIP) of whole-body 18F-FDG PET. The primary lesion on the medial part of the right breast is visible, and multiple lymphoma lesions are identified in the right arm, right hip and the lower left leg.

TABLE 1. Cotswolds Modification of Ann Arbor Staging System.

Stage	Area of Involvement
I	Single lymph node group
II	Multiple lymph node groups on same side of diaphram
III	Multiple lymph node groups on both sides of diaphram
IV	Multiple extranodal sites or lymph nodes and extranodal disease
X	Bulk >10cm
E	Extranodal extension or single isolated site of extranodal disease
A/B	B symptoms: weight loss >10%, fever, drenching night sweats

From: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Hodgkin's Lymphomas. March 27, 2014. www.nccn.org, website consulted on May 1, 2017.

DISCUSSION

DIAGNOSIS OF BREAST IMPLANT-ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA

Patients with a breast implant who at clinical examination present a breast swelling, adjacent mass or persistent skin rash in front of the breast, need further examinations after a clinical evaluation.

The first key radiological exam is the breast ultrasound (US) performed to detect the presence of any fluid collection and identify any associated capsule mass. Of note, all implants can have a normal peri-prosthesis seroma, but any delayed seroma (more than one year after the surgery) that cannot be explained by a breast trauma or an infection warrants an investigation for BIA-ALCL.[4] US is more useful than a mammography and similar and better than computed tomography or magnetic resonance imaging for detecting a mass or an effusion in BIA-ALCL.[4]

After the US, aspiration of the fluid by fine-needle aspiration should be performed. A suspicious mass will also require a tissue biopsy. Cytological examination of the seroma followed by immunohistochemistry is required.[4] Immunohistochemistry is essential for the diagnosis of BIA-ALCL.[12] Morphologically, the tumour is composed by large pleomorphic cells with abundant cytoplasm and horseshoe-shaped nucleus with prominent nucleoli ('hallmark cells').[4] At immunohistochemistry, CD30 must be positive and ALK negative.[6] T-cell antigens are expressed variably and at a lower frequency, with the most common being CD4 (80-84%), CD43 (80-88%), CD3 (30-46%), CD45 (36%) and CD2 (30%). Expression of CD5, CD7, CD8 and CD15 is uncommon.[4]

STAGING OF BREAST IMPLANT-ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA

When the diagnosis of BIA-ALCL is confirmed, a PET-CT scan is useful to demonstrate associated local masses and chest wall involvement and to evaluate the loco-regional and distant extension.[12]

There are two main staging systems that can be used for BI-ALCL: the Ann Arbor staging system (*Table 1*) and the tumour, lymph node, metastasis (TNM) staging system adapted from the MD Anderson (MDA; *Table 2*).

The traditional staging for all lymphoma is the Ann Arbor classification. Using this staging system, the majority of patients have low-stage disease IE (83-84%) or stage IIE (10-16%) versus stage IV disease (0-7%).[12]

Nonetheless, BIA-ALCL is not a classical non-Hodgkin lymphoma. In fact, BIA-ALCL usually progress locally and/or regionally like a solid tumour. This spread is better suited to the TNM system for staging solid tumours. Therefore, the MDA TNM staging system may be more applicable for predicting a prognosis and for evaluating treatment regimens in patients with BIA-ALCL.

TREATMENTS OF BREAST IMPLANT-ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA

As previously discussed, most cases have an indolent course.

- For all patients with BIA-ALCL, the first treatment must include a complete surgical excision of the breast lymphoma, the removal of the breast implant and a complete capsulectomy.[7] In the case of two breast implants, it is

TABLE 2. The MD Anderson solid tumour breast implant-associated anaplastic large cell lymphoma tumour, lymph node, metastasis (TNM) staging system.

Staging				
Tumour size	T1	T2	T3	T4
T	Confined to effusion	Early capsule invasion	Mass aggregate, confined to capsule	Tumour locally invasive out of capsule
Lymph Nodes	N0	N1	N2	
N	No lymph node involvement	One regional lymph node	Multiple regional lymph nodes	
Metastasis	M0	M1		
M	No distant spread	Other organs/distant sites		
Stages				
Stage IA : T1N0M0		Stage IIA : T4N0M0		Stage III : TanyN2M0, T4N1M0
Stage IB : T2N0M0		Stage IIB : T1-3N1M0		Stage IV : TanyNanyM1
Stage IC : T3N0M0				

From: Clemens MW, Horwitz SM. NCCN consensus guidelines for the diagnosis and management of breast implant-associated anaplastic large cell lymphoma. Aesthet Surg J. 2017;37(3):285-9.

also recommended to remove the contra-lateral implant to avoid a further dissemination. For patients with localised disease (Ann Arbor stage IE, MDA IA-IIA), the surgical therapy alone, without additional treatment, provides definitive therapy and cure in the majority of cases.[12] Actually, there are no predictive risk factors to identify patients who might benefit from adjuvant therapy.

- For patients with an incomplete excision, inadequate local surgical control or disseminated disease (Ann Arbor stage IIE-IV, MDA IIB -IV), additional treatment is required. Because of the limited data for these cases, the usual treatments and guidelines are actually not well defined, and according to the National Comprehensive Cancer Network (NCCN), the management should be individualised.[13]
- Patients with local residual disease, positive margins or unresectable disease with chest wall invasion may benefit from radiation therapy when feasible.[11]
- For confirmed extended disease with lymph node involvement (MDA IIB-IV) according to NCCN guidelines, patients should receive poly-chemotherapy such as for systemic ALCL ALK-negative.[13] The usual adjuvant therapy is an anthracycline-based chemotherapy CHO(E)P for six cycles. Recently, brentuximab vedotin showed promising results in patients with recurrent ALCL.[8] Brentuximab vedotin is an antibody-drug conjugate consisting of a chimeric anti-CD30 monoclonal antibody attached to a microtubule inhibitor via a linker. Once bound to CD30, brentuximab vedotin exerts an anti-tumour activity.[14] Some encouraging case reports demonstrating complete remission after the use of brentuximab vedotin for the treatment of BIA-ALCL in the context of refractory disease were published.[8] In addition, brentuximab vedotin is better tolerated with fewer side effects than standard chemotherapy. Evaluation of brentuximab vedotin as first-line treatment for advanced BIA-ALCL has not yet been performed.[8]

FOLLOW-UP OF BREAST IMPLANT-ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA

Follow-up schedules consisting of history and physical examination every three months for one year, every six months for two additional years and once a year until five years are

KEY MESSAGES FOR CLINICAL PRACTICE

1 **Breast implant-associated anaplastic large cell lymphoma is a recently described new T-cell lymphoma associated with breast implants used after breast cancer or for cosmetic reasons.**

2 **The diagnosis is sometimes difficult, and clinicians should be aware of this rare new entity.**

3 **The outcome of this lymphoma is generally good after implant removal, but extended disease will require chemotherapy.**

4 **Breast implant-associated anaplastic large cell lymphoma should be declared to Belgian health authorities.**

usual practice, as is a CT-scan at six, twelve and twenty-four months. However, there is no evidence that routine imaging in patients in complete remission provides any outcome advantage in T-cell lymphomas.

CONCLUSION

BIA-ALCL is an unusual complication of a breast implant and a cancer with a low mortality rate because the majority of cases are following an indolent course. We report here a case of extended BIA-ALCL successfully treated with CHOP. According to published guidelines, the diagnosis should be discussed and complementary exams performed if swelling of the breast, peri-prosthetic skin effusion or persistent redness associated with a breast implant appeared.

The first complementary exam is US, and any delayed seroma identified must be investigated by a cytology examination and immunohistochemistry (CD30 and ALK). The disease extension is evaluated by a PET-CT scan.

The first treatment for local or disseminated forms is a total breast implant removal. In most cases, only surgery is indicated.

For locally unresectable masses or partially removed tumour, radiotherapy is indicated. For extended disease, adjuvant chemotherapy like CHOP is recommended. Recently, brentuximab vedotin, a chimeric anti-CD30 monoclonal antibody, has shown encouraging results in the treatment of refractory BIA-ALCL.

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