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Locally advanced breast implant-associated anaplastic large-cell lymphoma: a combined medical-surgical approach

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Abstract. – OBJECTIVE: Breast implant-associated anaplastic large-cell lymphoma (BIA-ALCL) is a rare form of non-Hodgkin's T-cell lymphoma that develops around breast implants.

CASE PRESENTATION: This report illustrates the case of a patient affected by a locally advanced BIA-ALCL which infiltrated the thoracic wall (stage T4N0M0) following implant-based reconstruction after left mastectomy. Given the initial inoperability due to the patient's poor general condition, the treatment plan provided for a primary cycle of systemic neoadjuvant immunotherapy/chemotherapy, surgical removal of the mass, and subsequent systemic chemotherapy/immunotherapy. This resulted in complete remission – the patient remained disease-free even over a year later – without the need for adjuvant radiotherapy.

CONCLUSIONS: Our real-life case shows how the existing guidelines can be successfully adapted as part of an individualized approach to advanced and/or difficult cases.

Key Words:
BIA-ALCL, Breast implant anaplastic cell lymphoma, Textured breast implant, Neoadjuvant therapy in BIA-ALCL.

Introduction

Breast implant-associated anaplastic large-cell lymphoma (BIA-ALCL) is a rare form of non-Hodgkin's T-cell lymphoma that develops in the scar tissue (capsule) around the breast implant[1]. Generally, surgical removal of the breast implant and scar tissue is sufficient for total remission. However, in more advanced cases, the lymphoma may spread to the lymph nodes surrounding the breast and can even become fatal[2]. BIA-ALCL has recently been recognized by the World Health Organization (2016), after previous acknowledgement by Food and Drug Administration (2011). However, the discussion on the appropriate treatment for this relatively new pathology remains open.

In this report we illustrate our multidisciplinary approach to a case of stage T4N0M0 locally advanced BIA-ALCL with infiltration of the chest wall. This approach involved a combination of medical and surgical care strategies tailored to the patient's compliance and systemic clinical condition.

Case Presentation

We report the case of a patient who underwent prosthetic reconstruction in 2007 *via* Allergan macro-textured implant following left mastectomy, who presented in October 2019 with an advanced, ulcerated and necrotic neoformation at the breast reconstruction site (Figure 1A). She underwent diagnostic biopsy, which indicated a lymphoproliferative disease. Histology showed fibroadipose tissue infiltrated by a poorly differentiated neoplasm, largely necrotic, consisting of large, atypical cells with a fair amount of cytoplasm (Figure 2A). Immunohistochemically, the neoplastic cells were positive for CD45, CD4, CD30 (Figure 2B), and MUM1/IRF4, but negative for pan-cytokeratin stain (CKAE1/AE3), melanoma markers, and ALK-1, CD20, CD21, CD3, CD5 and CD8. A diagnosis of BIA-ALCL was made based on the clinical data, morphology and immunophenotype.

At this point, PET-CT staging showed locally advanced disease, involving the 5th, 6th and 7th left ribs, but no lymph node involvement or remote metastases (Figure 3A). The poor clinical

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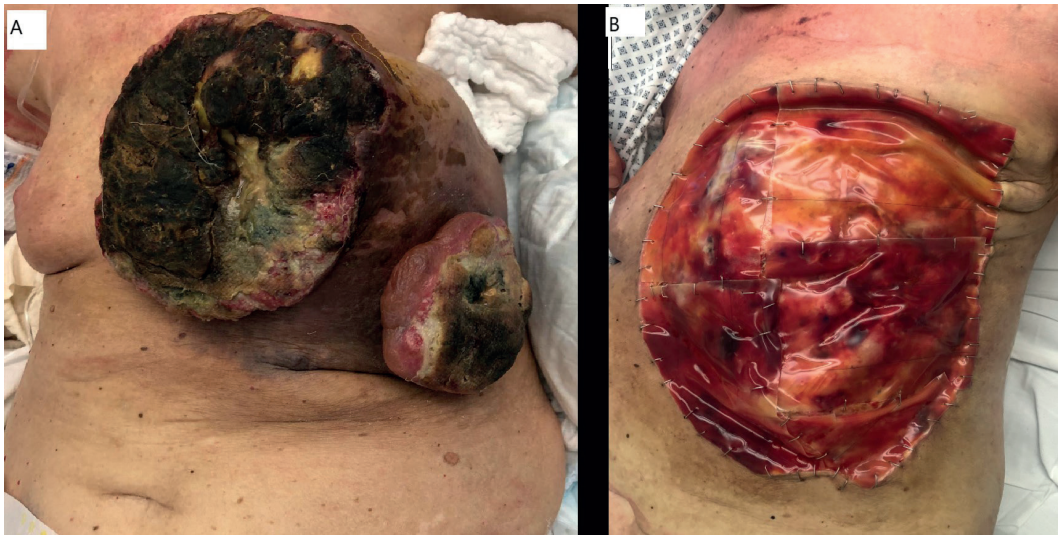

Figure 1. Left breast completely subverted by a double ulcerated and necrotic neoformation (**A**). 20 days post-operative view after tumor removal (**B**).

condition of the patient (heart failure with double basal pleural effusion) ruled out the possibility of radical surgery at the time of diagnosis.

Hence, administration of anti-CD30 monoclonal antibody brentuximab vedotin 100 mg combined with neoadjuvant administration of vincristine 1 mg was begun, with the aim of shrinking the mass. At the same time, appropriate treatments were administered to improve the patient's general condition and make her eligible for surgery to remove both the tumour and the prosthesis *en masse*. The decision to undertake immunotherapy as a first-line therapy, as opposed to the polychemotherapy indicated by the COMP scheme (cyclophosphamide, liposomal doxorubicin, vincristine, prednisone and rituximab) prescribed by Italian ministerial guidelines[3], was made to avoid exposing the patient – who was already suffering from congestive heart failure – to the cardiotoxic effects of chemotherapy drugs, which could have further delayed surgery.

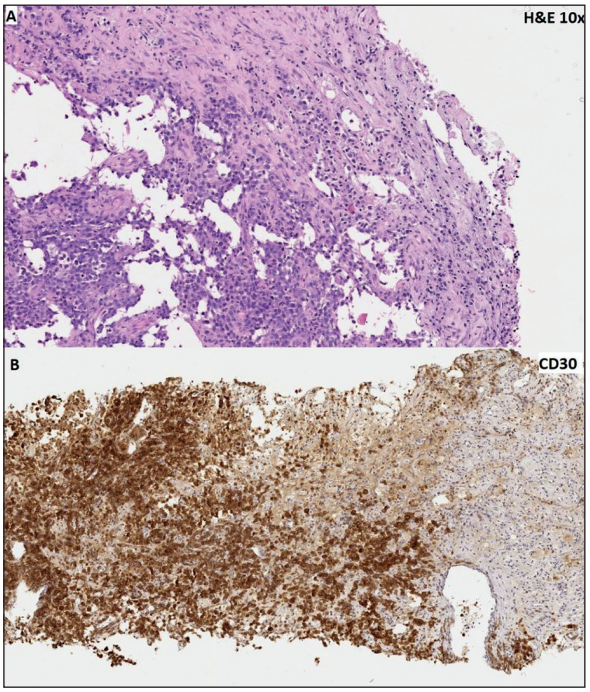

Figure 2. Histology showing a poorly differentiated neoplasm, consisting of large, atypical cells with a fair amount of cytoplasm (**A**). Immunohistochemically, the neoplastic cells showed positivity for CD30 (**B**).

On 29th October 2019, the patient underwent surgical removal of both the mass and the breast implant, sparing the thoracic wall and using dermal substitute for coverage (Figure 1B).

Upon gross examination, there were two exophytic ulcerated lesions on the skin surface, measuring 12x10 cm and 5.5x5 cm, respectively. Upon incision, we noted a fibrous capsule partially covering the prosthesis, which was intact. The removed tissue showed an almost completely necrotic-haemorrhagic neoplasm, which involved the fibrous capsule, the skeletal muscle tissue, and focally the skin, which was ulcerated. The excision was conducted "*in sano*", with a generous surgical margin (roughly 3 cm). Good cleavage from the thoracic wall was achieved, but some adherence remained on the 5th, 6th and 7th ribs. Perichondral biopsies were performed on this

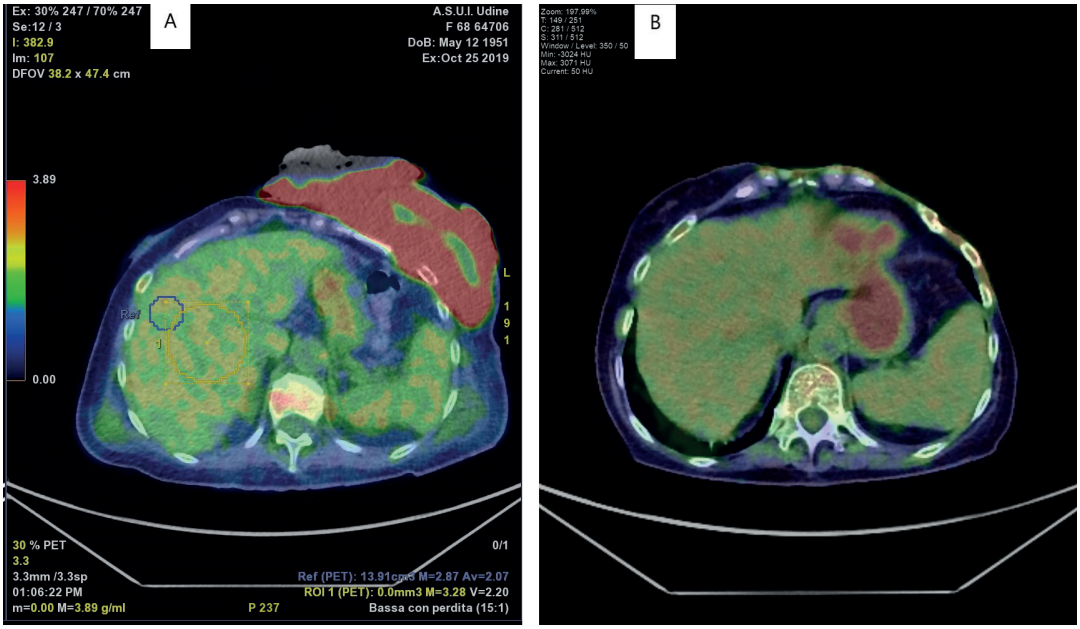

Figure 3. PETCT-scan image showing the mass involving the ribs (**A**). 3 months post-operative PETCT-scan image showing no residual disease (**B**).

adherent tissue (precisely where PET-CT scan showed involvement) to rule out tumour involvement. The surgery was completed successfully, with no peri-operative or post-operative complications.

Histology confirmed the earlier diagnosis of BIA-ALCL, which had been completely removed, without rib involvement. The patient was categorized as having pT4, N0, stage IIA disease[4]. In view of the favourable post-intervention course and the absence of surgical complications, 2 weeks after surgery, it was decided to continue the plan to administer immunochemotherapy *via* two full doses of brentuximab vedotin (100 mg on 16/11/2019 and 07/12/2019), and two cycles of COMP polychemotherapy (the first fractionated over the 7th and 8th of November 2019, and the second from the 28th to 29th of the same month). Vincristine was omitted from the second cycle in order not to increase the risk of neurological toxicity from brentuximab vedotin. During her stay, the patient remained apyretic, and no significant infectious complications occurred. At the end of December 2019, she was continued on the polychemotherapy and immunotherapy programme, receiving the third cycle of COMP polychemotherapy (fractionated from the 28th to 29th, omitting the dose of vincristine), followed by the fourth administration of brentuximab vedotin 100 mg on the 30th). The treatment scheme is summarized in Table I. PET-CT control, carried out in January 2020, showed that the ribs remained clear of involvement (Figure 3B).

In February 2020, multiple surgical biopsies of the thoracic wall were performed, which were negative for focal disease. In addition, the fourth cycle of COMP polychemotherapy was administered (fractionated from the 1st to the 2nd of February, omitting vincristine), followed by the fifth administration of brentuximab vedotin 100 mg on the 3rd of February 2020. In March 2020, the fifth cycle of COMP polychemotherapy was administered (fractionated over two days, omitting vincristine), followed two days later by the sixth dose of brentuximab vedotin (100 mg on the 5th of March). While she was receiving chemotherapy, the patient was continuously examined and monitored *via* echocardiography, electrocardiogram, and electrolyte and enzyme level tests. Beta-blockers and diuretics were given as cardioprotective therapy, and liposomal formulations and fractionated administrations were used to reduce the risk of cardiotoxicity, as well as the cumulative dose. One month after finishing chemo/immuno-therapy she underwent skin grafting.

The patient was still in remission at over a year after diagnosis but died at the end of 2020 due to cardiovascular complications.

Table I. Chemo/immuno-therapy scheme combined with surgeries.

	22/10/2019	Vincristine 1 mg
1°	26/10/2019	Brentuximab Vedotin 100 mg
	29/10/2019	Surgery
1°	7-8/11/2019	COMP* polychemotherapy
2°	16/11/2019	Brentuximab Vedotin 100 mg
2°	28-29/11/2019	COMP* polychemotherapy (omitting vincristine)
3°	07/12/2019	Brentuximab Vedotin 100 mg
3°	28-29/12/2019	COMP* polychemotherapy (omitting vincristine)
4°	30/12/2019	Brentuximab Vedotin 100 mg
4°	1-2/02/2020	COMP* polychemotherapy (omitting vincristine)
5°	3/02/2020	Brentuximab Vedotin 100 mg
	25/02/2020	Surgery: multiple biopsies of the thoracic wall
5°	3/03/2020	COMP* polychemotherapy (omitting vincristine)
6°	05/03/2020	Brentuximab Vedotin 100 mg
	06/04/2020	Surgery: skin grafting

*COMP: cyclophosphamide, liposomal doxorubicin, vincristine, prednisone and rituximab.

Discussion

The clinical case in question describes a state of advanced disease in a patient suffering from several comorbidities. It therefore required an individualized approach, while still adhering to current ministerial and international guidelines.

From the moment this disease was first identified[5], the standardization of care for patients with BIA-ALCL has evolved. However, the importance of complete surgical excision was immediately understood[2]. New guidelines from the National Comprehensive Cancer Network (USA) regarding BIA-ALCL[4] confirm that timely diagnosis and complete surgical removal of the lymphoma and the surrounding fibrous capsule is the optimal approach for managing patients with this disease. So, when it is not possible to achieve complete excision, or if there is thoracic wall involvement (stage II and above), a combination of several approaches should be considered in addition to surgery: namely radiotherapy, chemotherapy and/or immunotherapy[6]. The latter, specifically with brentuximab vedotin – a drug-antibody conjugate with a chimeric CD30 antibody attached to a microtubule inhibitor – has opened new frontiers and is increasingly being recognized as a successful treatment for BIA-ALCL[7]. Indeed, clinical trials in CD30-positive recurrent or refractory anaplastic large-cell lymphoma demonstrate that it provides a lasting response and tumour regression in most patients[8,9]; its use in combination with chemotherapy as first-line therapy for T-cell lymphoma yielded an overall response rate of 86% and complete remission in 57% of patients[10].

As a systemic treatment, the ministerial guidelines recommend CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone) or DA-EPOCH (dose-adjusted etoposide, doxorubicin and cyclophosphamide with vincristine, prednisone and rituximab) as a first-line therapy. Considering the cardiotoxicity of above regimens, COMP with non-pegylated liposomal doxorubicin was selected for this patient, with the aim to reduce cardiotoxicity without lessening the efficacy[11]. Chemotherapy was postponed until after surgery, because administering it beforehand could have compromised the feasibility of surgery itself.

Instead, our patient was given immunochemotherapy for neoadjuvant purposes prior to surgery. Specifically, vincristine 1 mg and anti-CD30 monoclonal antibody brentuximab vedotin 100 mg were administered. Although this approach is not precisely codified in the guidelines, it provoked a rapid reduction in tumour mass. This enabled surgical cleavage on the costal plane, making it possible to perform an excision that was "unexpectedly" radical. The response to this approach – which proved to be entirely favourable for over a year, at least – itself provides important prognostic information about the control of BIA-ALCL. The alternating administration of polychemotherapy cycles according to the COMP scheme and anti-CD30 monoclonal antibody led to disease remission without having to resort to radiotherapy and its associated toxic accumulation effects.

Only one other case in which neoadjuvant therapy was administered in the treatment of BIA-ALCL, suggesting a role for its use in advanced disease, is reported in the literature[12]. Our case too indicates a role for neoadjuvant chemotherapy and immunotherapy in the treatment of advanced BIA-ALCL. This approach warrants consideration in selected cases in which radical surgery is not possible or precluded due to the general condition of the patient. Our outcome makes a case for adapting the existing guidelines in advanced and/or difficult cases, as part of an individualized and multidisciplinary approach. In the pandemic era, an assiduous and constant dialogue between specialists and the institutions (i.e., the Ministry of Health, Italy) should be maintained to this end, although the aid of multimedia resources[13].

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Statement of Ethics

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee for studies involving human participants, and with the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards. Written informed consent was obtained from the patient's kin for publication of this case report and any accompanying images.

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