Breast implant-associated anaplastic large-cell lymphoma and the role of brentuximab vedotin (SGN-35) therapy: A case report and review of the literature

KRISTIN RICHARDSON[1], TAHA ALRIFAI[1], KELLY GRANT-SZYMANSKI[2], GEORGE J. KOURIS[3], PARAMESWARAN VENUGOPAL[2], BRETT MAHON[4] and REEM KARMALI[2]

[1]Rush University Medical Center; [2]Division of Hematology, Oncology and Cell Therapy; Departments of [3]Plastic and Reconstructive Surgery and [4]Pathology, Rush University Medical Center, Chicago, IL 60612, USA

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Abstract. Breast implant-associated (BIA) anaplastic large-cell lymphoma (ALCL) is a rare disease, comprising a small percentage of all non-Hodgkin lymphomas (NHLs), reportedly 2-3%. There is currently no established standard approach to the treatment of BIA ALCL. The first case on the development of ALCL in the presence of a breast implant was reported in 1997 and the association was first identified by the Food and Drug Administration in 2011. We herein describe a case of BIA ALCL in a patient with a previous history of breast cancer and breast reconstruction who presented with hardening of her breast implant. The patient underwent capsulectomy and the findings of the pathological examination were consistent with ALCL. The patient completed three cycles of combination chemotherapy consisting of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP regimen) followed by radiation consolidation therapy, and has maintained a complete remission ever since. The aim of the present study was to review the treatment options for BIA ALCL and suggest an investigation of the CD30-directed antibody-drug conjugate, brentuximab vedotin, as a potential treatment option for BIA ALCL.

Introduction

Anaplastic large-cell lymphoma (ALCL) is described as an aggressive subtype of T-cell lymphoma exhibiting strong expression of the cytokine receptor CD30. Amongst lymphoid neoplasms, ALCL comprises a small percentage of all non-Hodgkin lymphomas (NHLs), reportedly 2-3% (1). There are two major variants of ALCL based on the presence or absence of anaplastic lymphoma kinase, namely ALK-positive vs. ALK-negative, the latter typically holding a poorer prognosis. ALCL has a strong tendency to involve the bone marrow and other extranodal sites, including the skin, bone and soft tissues; however, it rarely involves the breast. An association between breast implants and ALCL has been described, with the first such case published by Keech and Creech in 1997 (2). Since that time, according to the Food and Drug Administration records and a recently published study by Clemens *et al*, there have been a total of 87 reported cases of breast implant-associated (BIA) ALCL worldwide (3,4). The aim of the present study was to present an additional case of BIA ALCL, provide an overview of various explored treatment modalities for this type of tumor, further highlight the characteristic CD30 positivity of ALCL and suggest the role of brentuximab vedotin within this patient population.

Case report

A 55-year-old woman was diagnosed with right-sided breast cancer in 1998. At the time of diagnosis, the patient underwent mastectomy followed by breast reconstruction with a flap and saline implant, adjuvant chemotherapy with cyclophosphamide with doxorubicin and 5 years of maintenance with anastrozole.

Over 10 years following breast reconstruction, the patient presented to her plastic surgeon with complaints of hardening of the skin over the right breast implant. The physical examination revealed gross asymmetry of the reconstructed breast in addition to significant discomfort on palpation, consistent with severe capsular contracture. A decision was made to perform a capsulectomy and replace the saline implant. During the procedure, a thick rind of capsule in addition to an old hematoma was discovered in the breast pocket. The existing implant was deflated and removed followed by evacuation of the hematoma and circumferential capsulectomy. A silicone implant was then placed.

The right breast capsule was sent for pathological evaluation. On microscopic examination, the capsule was fibrous with a rim of large pleomorphic cells, with abundant mitotic figures

Correspondence to: Dr Reem Karmali, Division of Hematology, Oncology and Cell Therapy, Rush University Medical Center, 1725W Harrison Street, Suite 809, Chicago, IL 60612, USA
E-mail: reem_karmali@rush.edu

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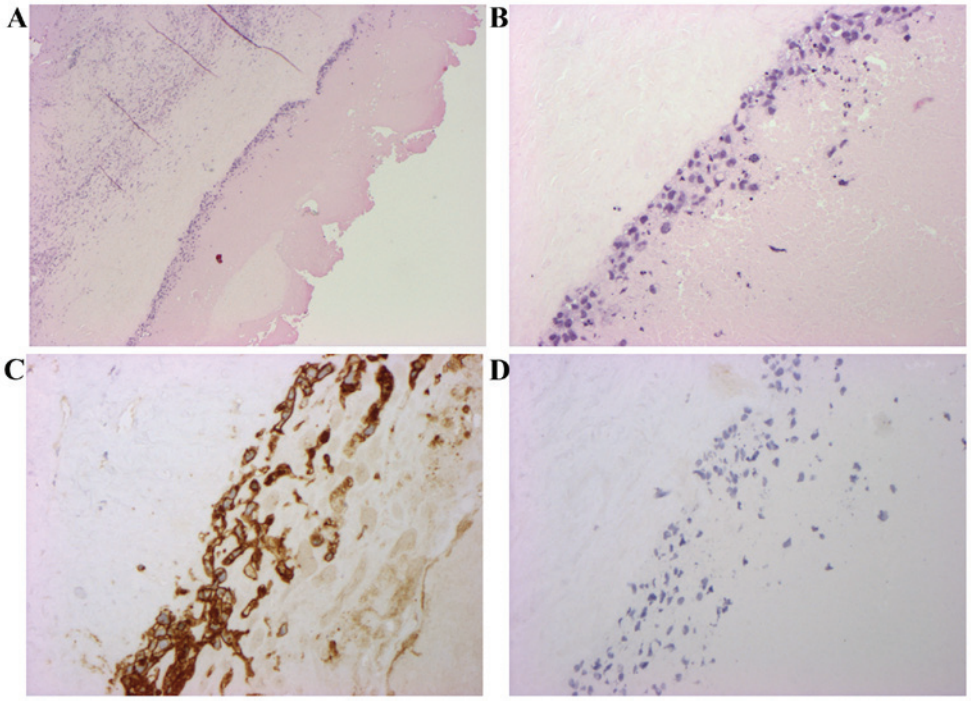

Figure 1. Pathological examination of the right breast capsule. (A) Fibrous capsule with a rim of large pleomorphic cells [hematoxylin and eosin (H&E) staining; magnification, x40]; (B) large pleomorphic cells with abundant mitotic figures and necrosis (H&E staining; magnification, x200); (C) the neoplastic cells stained strongly for CD30 (magnification, x200); and (D) the neoplastic cells stained negative for anaplastic lymphoma kinase (magnification, x200).

and necrosis (Fig. 1A and B). These cells stained positive for CD30 (Fig. 1C) and negative for ALK (Fig. 1D), CD4, CD5, CD8, CD3, CD20, cytokeratin 8/18, CD68 and E-cadherin.

Based on the clinical history, the morphological findings and immunostaining profile, the final pathology was consistent with ALK-negative BIA ALCL. The patient was then referred to the Department of Hematology/Oncology. She underwent a staging positron emission tomography (PET)/computed tomography (CT) scan, which revealed a small hypermetabolic soft tissue focus anterior to the right breast implant, with an additional focus of hyperactivity in the colon. A colonoscopy with biopsy revealed a small polyp with benign pathological characteristics. The bone marrow biopsy was also negative for lymphoma. For the management of localized BIA ALCL, the patient returned to the operating room for removal of the silicone implant that was placed at the time of the initial capsulectomy; after surgery, she was initiated on an abbreviated course of chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP regimen) for a total of three cycles, followed by radiation consolidation. A post-treatment PET/CT revealed minimal hyperactivity at the site of the resected breast implant, most likely associated with postoperative changes. The patient has maintained a complete remission since completion of therapy in 2014, with the most recent surveillance PET/CT in December, 2015 and the most recent clinical follow-up in April, 2016.

Discussion

BIA ALCL is a rare disease and little is known on the biology of these tumors. Among reported cases, less than half of the patients had a prior history of breast cancer. Additionally, there appears to be no established measure of risk with regards to the type of implant, as the number of cases with silicone implants nearly equals that of saline implants. The incidence of this disease also remains unclear. Miranda *et al* suggested this is largely attributed to a lack of standardization regarding pathological examination of mammary implants, with the majority of the institutions recommending gross examination alone (5).

Patients diagnosed with BIA ALCL present with either an effusion or a mass contiguous to the breast implant, with effusion being the most common presentation (6). Based on the available cases of BIA ALCL, there is a median of 9 years from implant placement to lymphoma diagnosis. All reported tumors tested strongly positive for CD30 and nearly all were ALK-negative (4,5). Although the majority of cases are described as having an indolent course, a small percentage have an aggressive course, typically in association with a mass at diagnosis. Taken collectively, the biology of BIA ALCL along with the clinical presentation and disease course appear to be quite different from that of systemic ALK-negative ALCL.

There is no standard approach to the management of BIA ALCL, given the rarity of this disease. A variety of treatment options have been described for this entity, ranging from surgery (capsulectomy with or without lymph node dissection) with surveillance vs. surgery with chemotherapy or radiation or a combination of the above. A few reports have also investigated stem cell transplantation. The chemotherapeutic regimens have included CHOP, CHOP with etoposide (CHOEP), ifosfamide, carboplatin and etoposide (ICE) and hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone (Hyper-CVAD) regimens. As previously

Table I. Recent and ongoing trials using brentuximab in ALCL and CD30+ T-cell lymphomas in the first-line and salvage setting.

Studies involving brentuximab (anti-CD30) and ALCL	Sample size	Regimen/arms	Results	Refs.
Brentuximab vedotin and bendamustine for the treatment of HL and ALCL NCT ID 1657331	N/A	Single-arm phase I/II study	Ongoing	(8)
ECHELON-2: A comparison of brentuximab vedotin and CHP with standard CHOP in the treatment of patients with CD30+ mature T-cell lymphomas NCT ID 1777152	N/A	Brentuximab + CHP vs. CHOP, double-arm phase III study	Ongoing	(9)
Brentuximab vedotin + rituximab as front-line therapy for patients with CD30+ and/or EBV+ lymphomas NCT ID 1805037	N/A	Single-arm phase I/II study	Ongoing	(10)
Brentuximab vedotin or crizotinib and combination chemotherapy in treating patients with newly diagnosed stage II IV ALCL NCT ID 1979536	N/A	Brentuximab + combination chemotherapy vs. crizotinib + combination chemotherapy, double-arm phase II study	Ongoing	(11)
Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic ALCL: Results of a phase II study	N=58	Single-arm phase II study	-ORR: 86% -CR: 57% -PR: 29% -PFS: 13.3 months -OS: N/A	(7)
Brentuximab vedotin in the front-line treatment of patients with CD30+ peripheral T-cell lymphomas: Results of a phase I study	N=39 (total) N=32 (ALCL)	Brentuximab followed by CHOP vs. brentuximab + CHP, double-arm phase I study	Arm 1 -ORR: 85%, CR: 62%, PR: 23%, 1-year PFS: 77%, OS: 85% Arm 2 -ORR: 100%, CR: 84%, PR: 16%, 1-year PFS: 71%, OS: 88%	(12)
Phase I/II study of brentuximab vedotin in Japanese patients with relapsed or refractory CD30+ HL or systemic ALCL	N=20 (total) N=5 (ALCL)	Single-arm phase I/II study	For ALCL patients -ORR: 100% -CR: 80%, -PR: 20% -PFS: 10.5 months	(13)
Retreatment with brentuximab vedotin in patients with CD30+ hematological malignancies	N=28 (total) N= 8 (ALCL)	Single-arm phase II study	For ALCL patients -ORR: 88%, -CR: 63%-PR: 25%, -PFS: 12.9 months	(14)

ALCL, anaplastic large-cell lymphoma; HL, Hodgkin lymphoma; EBV, Ebstein-Barr virus; ORR, overall response rate; CR, complete response; PR, partial response; PFS, progression-free survival; OS, overall survival; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CHP, cyclophosphamide, hydroxydaunorubicin, and prednisone.

described, there is a wide spectrum of disease severity, with a significant number of cases exhibiting an indolent course managed with surgery alone without disease recurrence, while fewer cases behave more aggressively and are refractory to multiple chemotherapy regimens (4,5,15). Within the scope of treatment for ALCL, brentuximab vedotin (SGN-35), an antibody-drug conjugate comprising an anti-CD30 antibody, has demonstrated encouraging outcomes in patients with recurrent ALCL (Table I). Additionally, brentuximab vedotin is generally well-tolerated, with a favorable side effect profile

compared with other standard chemotherapy options (7). To date, there has been one encouraging case report demonstrating complete remission after the use of brentuximab vedotin for the treatment of BIA ALCL in the context of refractory disease (15). The investigation of brentuximab vedotin in BIA ALCL is recommended, specifically in the first-line treatment setting as a way of circumventing more toxic options, such as standard chemotherapy.

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