Breast Implant–Associated Anaplastic Large Cell Lymphoma

Review of a Distinct Clinicopathologic Entity

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• Primary breast anaplastic large cell lymphoma (ALCL) is rare but is more commonly seen in patients with implants; fewer than 50 cases of breast implant–associated ALCL have been reported in the English language literature. Breast implant–associated ALCL is not a disease of the breast parenchyma, but instead is a disease of the fibrous capsule surrounding the implant. The patients usually present with an effusion around the implant and, rarely, with a solid mass. Morphologically, the neoplastic cells are large, epithelioid, and pleomorphic, with abundant cytoplasm, vesicular irregular nuclei, and frequent mitoses. Occasional "hallmark" cells may be present. The lesional cells typically show strong and diffuse immunoreactivity for CD30 and often express T-cell markers, cytotoxic-associated antigens, and epithelial membrane antigen. Almost all reported cases are negative for anaplastic lymphoma kinase. Molecular genetic analyses have demonstrated T-cell receptor gene rearrangements. The differential diagnosis essentially includes poorly differentiated carcinoma, other lymphomas, and chronic inflammation. Once a diagnosis of lymphoma is established, it is important to exclude systemic anaplastic lymphoma kinase–negative ALCL involving the breast, primary cutaneous ALCL, and other CD30$^+$ lymphoproliferative disorders. The patients with effusion-associated ALCL often have an indolent course and excellent prognosis, responding well to excision of the fibrous capsule around the implant (capsulectomy) and implant removal. In contrast, patients who present with a distinct mass may have a more aggressive course and poor prognosis, requiring chemotherapy and/or radiation therapy.

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Non-Hodgkin lymphomas (NHLs) can involve the breast, either as primary tumors or as dissemination from primary tumors outside of breast. Primary NHLs account for less than 1% of all breast malignancies. Most NHLs involving the breast are of B-cell origin, with diffuse large B-cell lymphoma being the most common type. Less than 10% of breast NHLs are of T-cell lineage.[1,2] Although anaplastic large cell lymphoma (ALCL), a rare T-cell lymphoma, accounts for only 3% of adult NHLs and 6% of breast NHLs,[1] it appears to have a tropism for the breast compared with other T-cell lymphomas.[2,3] Recent studies[3–6] have suggest a potential association between primary breast ALCL and breast implants, although others[7,8] have shown no increased risk of NHLs in women with breast implants. Although the odds ratio for ALCL associated with breast implants is reportedly 18.2, the absolute risk remains low because of the rarity of breast ALCL.[3] To date, fewer than 50 cases of breast implant–associated ALCL have been reported in the English language literature. Here we present a brief review of this entity, focusing on the salient clinicopathologic features and differential diagnosis.

CLINICAL FEATURES

The clinicopathologic characteristics of breast implant–associated ALCL cases reported in the literature are summarized in the Table. All patients are women, with a median age of 52 years (range, 28–87 years). The reasons for breast implants are cosmetic (59%) and reconstruction after breast-conserving surgery for mammary carcinoma (41%). The median time interval from implantation to diagnosis of ALCL is 8 years (range, 1–30 years). Local swelling is the most common presenting symptom, followed by pain, rash, pruritus, and pressure. Imaging studies typically show an effusion (also known as seroma) around the implant without (more often) or with a distinct mass (Figure 1). In contrast to other types of primary mammary lymphomas, which have a predilection for the right breast, ALCL equally affects both sides. The implants in these patients are either saline (58%) or silicone (42%), with no statistical significance in relation to ALCL.[6] Some studies have suggested that textured implants are more likely to be associated with late seromas than smooth-shell implants.[9]

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Clinical Characteristics of Reported Cases of Breast Implant–Associated Anaplastic Large Cell Lymphoma							
Patient No.	Source, y	Age, y	Reason for Implant	Time Interval, y	Clinical Presentation	Treatment	Outcome (Follow-up, y)
1	Keech and Creech,[18] 1997	41	Cosmetic	5	Mass	CT, RT	NED (1)
2	Gaudet et al,[19] 2002	50	Reconstruction	9	Mass	CT	Relapse/metastasis (1)
3	Gaudet et al,[19] 2002	87	Reconstruction	7	Mass	No treatment	NA
4	Sahoo et al,[20] 2003	33	Cosmetic	9	Effusion	CI, RT, CT	NED (1)
5	Fritzsche et al,[21] 2006	72	Reconstruction	16	Mass	No treatment	NA
6	Olack et al,[22] 2007	64	Reconstruction	7	Effusion	CI, CT, RT	NED (1.6)
7	Gualco et al,[23] 2009	28	Cosmetic	6	NA	NA	NA
8	Newman et al,[24] 2008	52	Cosmetic	14	Mass	CT, CI	NED (2)
9	Roden et al,[4] 2008	44	Cosmetic	NA	Effusion	CI	NA
10	Roden et al,[4] 2008	34	Cosmetic	4	Effusion	CI, RT, CT	NED (0.8)
11	Roden et al,[4] 2008	59	Reconstruction	3	Effusion	CI, RT	NED (0.8)
12	Roden et al,[4] 2008	45	Reconstruction	7	Effusion	CI	NED (1.7)
13	de Jong et al,[3] 2008	38	Cosmetic	13	NA	NA	NA
14	de Jong et al,[3] 2008	29	Cosmetic	7	NA	NA	NA
15	de Jong et al,[3] 2008	43	Cosmetic	13	NA	NA	NA
16	de Jong et al,[3] 2008	49	Cosmetic	23	NA	NA	NA
17	de Jong et al,[3] 2008	53	Cosmetic	1	NA	NA	NA
18	Wong et al,[25] 2008	40	Cosmetic	19	Mass	CI, CT, RT	NA
19	Miranda et al,[2] 2009	65	NA	NA	Effusion	NA	NA
20	Alobeid et al,[26] 2009	68	Reconstruction	16	Mass	CI, CT	AWD (0.3)
21	Bishara et al,[27] 2009	66	Reconstruction	7	Mass	CI, CT, RT	NED (3)
22	Li and Lee,[12] 2009	58	Reconstruction	5.5	Effusion	CI, CT	NED (0.8)
23	Lechner et al,[28] 2010	42	Cosmetic	3	Effusion	CI, RT	NED (0.6)
24	Popplewell et al,[5] 2011	32	Cosmetic	5	Effusion	NA	NA
25	Popplewell et al,[5] 2011	41	Cosmetic	5	Mass	CT, CI, RT, SCT	NED (6)
26	Popplewell et al,[5] 2011	54	Cosmetic	9	Mass	CI, CT, RT, SCT	NED (7.5)
27	Popplewell et al,[5] 2011	49	NA	NA	Mass	NA	NA
28	Popplewell et al,[5] 2011	62	Cosmetic	30	Mass	CI, CT, RT, alternative medicine	NA
29	Popplewell et al,[5] 2011	41	Cosmetic	12	Mass	CT, CI, RT	NA
30	Popplewell et al,[5] 2011	42	NA	NA	Mass	NA	NA
31	Popplewell et al,[5] 2011	49	Cosmetic	5	Effusion	NA	NA
32	Aladily et al,[6] 2012	57	Cosmetic	15	Mass	Radical mastectomy, CT	NED (0.5)
33	Aladily et al,[6] 2012	47	Reconstruction	9	Mass	CI, CT, RT	DOD (2)
34	Aladily et al,[6] 2012	63	Reconstruction	7	Mass	CI	DOD (12)
35	Aladily et al,[6] 2012	65	Cosmetic	29	Effusion	CI, CT, RT	NED (2)
36	Aladily et al,[6] 2012	63	Reconstruction	NA	Effusion	CI	NA
37	Aladily et al,[6] 2012	63	Reconstruction	10	Effusion	CI, CT, RT	NED (3)
38	Aladily et al,[6] 2012	46	Cosmetic	15	Effusion	CI	NED (2)
39	Aladily et al,[6] 2012	54	Cosmetic	11	Effusion	CI, CT, RT	NED (1)
40	Aladily et al,[6] 2012	39	Cosmetic	6	Effusion	CI	NED (0.5)
41	Aladily et al,[6] 2012	68	Reconstruction	14	Effusion	CI, RT	NED (1)
42	Aladily et al,[6] 2012	65	Reconstruction	19	Effusion	Mastectomy, axillary dissection	NED (2)
43	Aladily et al,[6] 2012	60	Reconstruction	4	Effusion	CI	NED (0.4)
44	Aladily et al,[6] 2012	47	Reconstruction	7	Effusion	Mastectomy, axillary dissection, CT, RT, SCT	NED (3.5)
45	Current case, 2013	68	Reconstruction	6	Mass	CT, CI	NED (1.6)

Abbreviations: AWD, alive with disease; CI, capsulectomy and implant removal; CT, chemotherapy; DOD, dead of disease; NA, not available; NED, no evidence of disease; RT, radiation therapy; SCT, stem cell transplant.

PATHOGENESIS

It has been accepted by many authorities, albeit not proved, that breast implant–associated ALCL is not a disease of the breast parenchyma, but instead is a disease of the fibrous capsule surrounding the implant.[10] A number of hypotheses have been proposed regarding its pathogenesis. Silicone has been shown to be immunogenic and to incite a chronic inflammatory response.[11] Saline implants are also often surrounded by an impermeable silicone elastomeric capsule that might be immunogenic by itself. Because chronic inflammation has been associated with development of lymphomas, such as *Helicobacter pylori* infection in gastric extranodal marginal zone lymphoma, it is possible that chronic inflammatory stimulation may be related to the development of breast implant–associated ALCL.[4,12] This is in keeping with the fact that ALCL originates from activated mature cytotoxic T cells.

PATHOLOGIC FINDINGS

Based on the gross findings, the patients can be divided into 2 groups: the first group presents with an effusion around the implant (seroma) without a grossly identified tumor mass (effusion-only group), whereas the second group presents with a distinct tumor mass (mass group). The estimated effusion volume ranges from 200 to 1000 mL. The effusion is typically fibrinoid and is contained within a

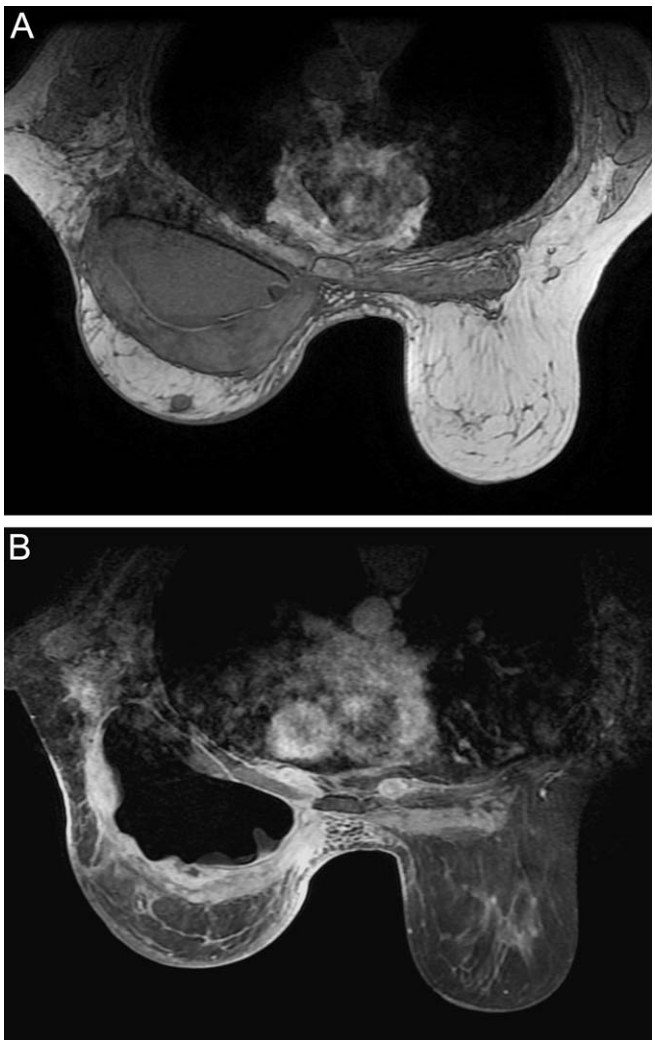

Figure 1. *Magnetic resonance (MR) images of a breast implant–associated anaplastic large cell lymphoma (Table, patient No. 45). Axial precontrast T1-weighted (A) and fat-suppressed T2-weighted (B) MR images demonstrate an enhancing mass completely surrounding the breast implant. The mass infiltrated the chest wall, abutting the pleura medially.*

thick fibrous capsule surrounding the implant.[2,3] The implants of effusion-only patients are usually grossly intact, and the fibrous capsule is uniformly thick with finely granular or fibrinoid inner lining. Abundant fibrinoid material is often identified on the side adjacent to the implant of the fibrous capsule. In patients with a mass, the implant has an irregular texture, and tumor mass protrudes from the fibrous capsule (Figure 1). Because breast implant–associated ALCL can be subtle and easily overlooked, it is important to carefully examine the gross specimen removed for implant-related complications.

Microscopically, the tumor cells are present in the effusion fluid or in the fibrous capsule of the implant. The cells in the effusion fluid are typically identified along the inner surface of the fibrous capsule, either as individual cells, as cell clusters, or occasionally as coherent sheets.[6] In cases of solid masses, the neoplastic cells are usually arranged in sheets in the background of variably fibrotic or sclerotic capsule on low magnification (Figure 2). Since these neoplastic cells arise from the capsule rather than the breast parenchyma, they should be at a distance from the breast parenchyma, at least at the early stage of disease. Geographic necrosis and sclerosis of the tumor mass can give a multinodular appearance. The tumor cells are large, pleomorphic, and discohesive, and have abundant pale to eosinophilic cytoplasm and irregular nuclei with dispersed chromatin and occasional prominent nucleoli. Yet the neoplastic cells can appear to be epithelioid, thus resembling poorly differentiated breast carcinoma. Occasionally, the lesional cells feature eccentric, horseshoe- or kidney-shaped nuclei and a paranuclear eosinophilic region. These cells have been referred to as "hallmark" cells. Mitoses are frequently seen. A variable degree of mixed inflammatory infiltrates composed of small lymphocytes, histiocytes, and eosinophils may be present in the background.

IMMUNOPHENOTYPE AND MOLECULAR GENETIC FINDINGS

Immunophenotyping is essential in diagnosing breast implant–associated ALCL.[6,13,14] The anaplastic cells characteristically show strong and uniform membranous expression of CD30. All reported cases, except one, are negative for anaplastic lymphoma kinase (ALK).[5] The tumor cells variably express T cell antigens including CD4 (80%–84%), CD43 (80%–88%), CD3 (30%–46%), CD45 (36%), and CD2 (30%), but have low or no expression of CD5, CD7, CD8, or CD15.[6,13] A subset of cases exhibits positivity for the cytotoxic-associated antigens such as T-cell intercellular antigen 1 (63%) and granzyme B (61%).[13] Approximately 40% to 70% of the cases are positive for epithelial membrane antigen, which, along with the pleomorphic histomorphology, may lead to an erroneous diagnosis of carcinoma. The proliferation index assessed with Ki-67 is typically high (>80%).[13] A recent study[13] has shown that BCL2 is strongly positive in breast implant–associated ALCL (91%), and thus may be a useful marker of this disease. Breast implant–associated ALCLs reportedly demonstrate rearrangements of T-cell receptor γ chain gene in most cases.[4,6]

DIFFERENTIAL DIAGNOSIS

The distinction between ALCL and chronic inflammation is generally not difficult, as the latter typically does not possess abundant CD30-positive, large, anaplastic cells. ALCL can have a cohesive architectural pattern that mimics carcinoma. Therefore, a recurrent or primary carcinoma needs to be ruled out with this finding. Lack of cytokeratin expression and immunoreactivity for CD30 and T-cell antigens (such as CD43 and CD4) are supportive of a diagnosis of ALCL. As previously mentioned, ALCL may be positive for epithelial membrane antigen. This finding, along with the high-grade morphology and negative hormonal receptor expression, may lead to a misinterpretation of triple-negative breast carcinoma. Thus, epithelial membrane antigen does not play a role in the differential diagnosis with carcinoma. Once a diagnosis of ALCL is established in a patient with a breast implant, it is important to distinguish whether the disease is dissemination from a systemic ALCL (especially the ALK-negative type),[1] a direct spread from an overlying primary cutaneous ALCL (C-ALCL), or a breast implant–associated ALCL, given their significantly different prognosis.

The aforementioned 3 entities are indistinguishable on morphologic grounds, as their phenotypes are very similar,

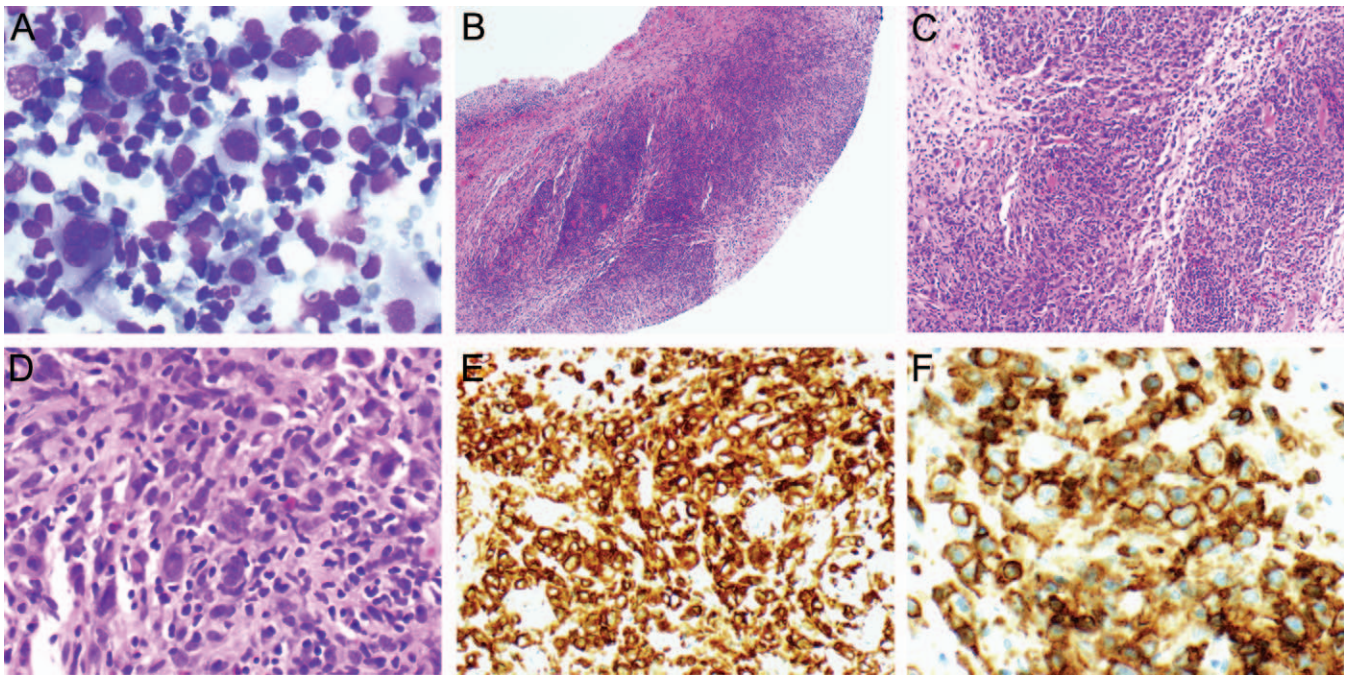

Figure 2. *Pathologic characteristics of the breast implant–associated anaplastic large cell lymphoma shown in Figure 1. Diff-Quik–stained fine-needle aspirate shows large pleomorphic neoplastic cells with abundant cytoplasm and irregular nuclei with dispersed chromatin and prominent nucleoli (A). Note a multinucleated cell and a cell with ringed nucleus. A low-power view of the biopsy shows fibrous capsule with extensive lymphoma infiltrate (B). Intermediate-power (C) and high-power (D) views reveal sheets of large, discohesive, markedly atypical cells with hyperchromatic or vesicular nuclei and occasional hallmark cells. The anaplastic cells exhibit strong and diffuse immunoreactivity of CD30 (E) and CD4 (F) (original magnifications ×400 [A and F] and ×200 [E]; hematoxylin-eosin, original magnifications ×40 [B], ×100 [C], and ×400 [D]).*

if not identical. However, other features, including age, site of involvement, ALK expression, and molecular genetic alteration, may be of help in distinguishing them. Systemic ALCL is characterized by an aggressive clinical course and should also involve nonbreast tissue (nodal and extranodal). It frequently expresses ALK subsequent to a reciprocal t(2;5) translocation, which results in fusion of the nucleophosmin (*NPM1*) and *ALK* genes. Anaplastic lymphoma kinase–positive systemic ALCL occurs most commonly in children and young adults and the 5-year survival rate is 60% to 80%, whereas ALK-negative systemic ALCL is more common in adults (40–65 years) and has a worse prognosis (5-year survival rate of 36%–48%).[15] In contrast to systemic ALCL, C-ALCL and breast implant–associated ALCL are more indolent. They are almost always ALK negative, and may be confused with ALK-negative systemic ALCL involving the breast. Therefore, a careful evaluation of clinical and radiologic findings is crucial. Cutaneous ALCL is more common in patients who present with ulceration and erythema of the skin. Patients with C-ALCL have no evidence of systemic disease for at least 6 months after presentation, and, in approximately 25% of patients, spontaneous regression occurs. Five-year survival for C-ALCL is greater than 95%.[16] Unlike systemic ALCL, C-ALCL expresses the cutaneous lymphocyte antigen and up to 40% express CD15, but do not express epithelial membrane antigen. Breast implant–associated ALCL arises in the fibrous capsule rather than the breast parenchyma or skin, and usually has fluid around the implant.

Other $CD30^+$ lymphomas such as classical Hodgkin lymphoma are also in the differential diagnosis of breast implant–associated ALCL, especially when ALCL loses T-cell/cytotoxic markers or when the tumor shows nodularity, sclerosis, or eosinophils and other inflammatory cells. Weakly positive PAX5 and CD15 and negative Epstein-Barr virus should strongly suggest the possibility of classical Hodgkin lymphoma. Although CD30 can be expressed by peripheral T-cell lymphoma, not otherwise specified, the pattern of CD30 staining is an important feature to distinguish it from breast implant–associated ALK-negative ALCL. In the latter, the CD30 expression should be strong and of equal intensity in all cells, whereas peripheral T-cell lymphoma expresses CD30 in at least a proportion of the cells and usually with variable intensity.

PROGNOSIS AND TREATMENT

The outcome data of breast implant–associated ALCL in the literature are limited because many reported cases have short follow-up intervals or are lost to follow-up (Table). A report[4] of 4 patients described this disease as an indolent T-cell proliferative disorder. Another study[5] has suggested that the disease course is not always indolent, with some patients relapsing in weeks to months after therapy and requiring multiple treatment regimens. A small number of patients have developed recurrent disease, and rare cases of death have been reported. A recent study[6] of 13 cases concludes that the clinical behavior of breast implant–associated ALCL is heterogeneous and depends on the type of disease. The patients who present with effusion without a distinct mass have an indolent disease course and the prognosis is excellent if the breast implant and fibrous capsule are removed. Those who present with a distinct mass may have more aggressive disease, including regional lymph node involvement and even death, and require chemotherapy and/or radiation therapy in addition to capsulectomy and implant removal.[6]

CONCLUSIONS

Although ALK-negative ALCL also occurs in the breast of patients without implants,[3,17] there has been increasing evidence supporting the association between primary ALK-negative ALCL and breast implants. Breast implant–associated ALCL is a rare tumor that is clinically and pathologically distinct from systemic ALK-negative ALCL and C-ALCL. This entity may need to be recognized as a separate category, which may provoke a revision of the World Health Organization Classification of Lymphoma.

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