Coming of Age

Breast Implant–Associated Anaplastic Large Cell Lymphoma After 18 Years of Investigation

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KEYWORDS

• Breast implant–associated ALCL • Anaplastic large cell lymphoma • Non-Hodgkin lymphoma • CD30

KEY POINTS

- Breast implant–associated anaplastic large cell lymphoma (BI-ALCL) is a distinct type of T-cell lymphoma involving the capsule or effusion surrounding a breast implant.
- BI-ALCL most commonly presents in two-thirds of cases as a delayed (>1 year) periprosthetic fluid collection and as a capsular mass in one-third of cases. One-in-8 patients presents with lymphadenopathy.
- Optimal screening tools include ultrasound or positron emission tomography (PET)/CT scan with directed fine-needle aspiration. Diagnosis should be made prior to surgical intervention.
- Tissue and fluid specimens from suspected cases should be sent with a clinical history to pathology to rule out anaplastic large cell lymphoma (ALCL).
- Operative treatment should include removal of the implant and resection of the entire capsule as well as complete excision of the disease and involved lymph nodes.
- The role of adjunctive treatments, such as chemotherapy, chest wall radiation, anti-CD30 immunotherapy, and stem cell transplant for advanced disease, is under investigation.

INTRODUCTION

In 2011, the United States Food and Drug Administration (FDA) published a safety communication stating, "Women with breast implants may have a very small but increased risk of developing anaplastic large cell lymphoma (ALCL) in the scar capsule adjacent to an implant."[1] This warning was based on case reports dating back to a sentinel case described by Keech and Creech in 1997.[2] The past 18 years have been marked by a transition from a few case reports of a novel periprosthetic T-cell lymphoma to the current understanding and recognition of BI-ALCL. The association of breast implants with a rare cancer of the immune system has created understandable concern among patients, surgeons, and oncologists; therefore, continued investigation is needed to determine which factors play a role in the

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malignant degeneration of a breast implant capsule. Several evolving concepts have helped define diagnostic tools, therapeutic strategies, and outcomes of BI-ALCL and are the focus of this article.

LYMPHOMA BACKGROUND

Lymphoma is a cancer of the immune system developing from lymphocytes and is the most common malignancy of the blood.[3] Lymphoma broadly includes Hodgkin lymphoma, non-Hodgkin lymphoma (NHL), multiple myeloma, and immunoproliferative diseases. In the United States, Approximately 65,000 cases of NHL were diagnosed in 2010.[4] Stein and colleagues[5] first described ALCL in 1985 as a novel type of NHL characterized by large anaplastic lymphoid cells that express the cell-surface protein CD30. Estimated incidence of T-cell NHL diagnoses in the United States in 2014 was 7000 to 10,000.[6] ALCL represents approximately 2% to 3% of all NHLs and approximately 20% of all T-cell lymphomas.[7]

ALCL was added as a distinct entity to the Kiel classification in 1988 and to the Revised European American Lymphoma Classification in 1994.[8] The World Health Organization (WHO) classification of lymphomas recognized the disease in 2001 and further delineated variants in their updated 2008 classification.[9,10] NHL prognosis is predicted using the International Prognostic Index (IPI) based on the presence of recognized risk factors, such as the Ann Arbor staging system, age, elevated serum lactate dehydrogenase, performance status, and number of extranodal sites of disease.[11] Clinicopathologic subtypes of ALCL include a spectrum of disease from the more aggressive systemic ALCL down to lymphoproliferative disorders, such as the relatively indolent skin-limited primary cutaneous ALCL (5-year OS >90%–95%) and benign lymphomatoid papulosis.[12] Multiple sites of disease, frequent lymphadenopathy, and metastatic spread characterize systemic ALCL. Systemic ALCL is classified by either the expression or absence of the anaplastic lymphoma kinase (ALK) tyrosine kinase receptor gene translocation. A 2;5 translocation involving the 2p23 and the 5q35 chromosome creates an oncogenic fusion protein of the ALK gene and the nucleophosmin gene.[13] ALK-positive ALCL accounts for approximately 50% to 80% of all ALCLs and occurs most commonly in men (male/female ratio: 6.5:1) under the age of 30 and has a 5-year OS by IPI point value of 0/1: 90%, 2: 68%, 3:33%, and 4/5: 23%.[5] In contrast, ALK-negative ALCL is an immunophenotypically and cytogenetically heterogeneous group and has a 5-year OS by IPI points 0/1: 74%, 2: 62%, 3:31%, and 4/5: 13%. Standard first-line chemotherapy is cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (CHOP); and refractory disease is treated with ifosfamide, carboplatin, and etoposide (ICE) or etoposide, methylprednisone, cytarabine, and cisplatin (ESHAP).[14] When treated with chemotherapy, ALK-positive ALCL has a higher 5-year overall survival (OS) rate than systemic ALK-negative ALCL (58% vs 34%, respectively).[15,16] As a percentage of all T-cell lymphomas, ALK-positive ALCL is more common in North America than Europe or Asia (16.0% vs 6.4% vs 3.2%, respectively). Systemic ALK-negative ALCL is more common in Europe than North America or Asia (9.4% vs 7.8% vs 2.6%, respectively).[17]

BREAST IMPLANT–ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA: A NOVEL VARIANT

BI-ALCL is distinct from primary breast lymphoma (PBL); PBL, in contrast, is a disease of the breast parenchyma, representing 0.04% to 0.5% of breast cancers and 1% to 2% of all lymphomas.[18] PBL is predominantly a B-cell lymphoma (65%–90%).[19,20] BI-ALCL is a purely T-cell lymphoma arising either in the effusion or scar capsule surrounding a breast implant.[21] All reported cases of BI-ALCL are ALK negative and express a CD30 cell-surface protein (**Figs. 1** and **2**). Most cases are diagnosed during implant revision surgery performed for a late-onset (>1 year), persistent seroma and may be associated with symptoms of pain, breast lumps, swelling, or breast asymmetry. The numbers of BI-ALCL cases reported in primary augmentation and reconstruction for breast cancer or prophylaxis are approximately equivalent. BI-ALCL most commonly follows an indolent course with disease regression after adequate surgical ablation alone without systemic therapy, but aggressive exceptions have been reported.[22] No risk factors have been clearly identified for ALCL although many have been theorized, including the presence of a subclinical biofilm, response to particulate from textured implants, a consequence of capsular contracture or repeated capsular trauma (such as with closed capsulotomies), genetic predisposition, or an autoimmune etiology, but these observations have not been confirmed in formal epidemiologic studies.[23] Recent studies have demonstrated a possible pathogenic mechanism of chronic T-cell stimulation with local antigenic drive, ultimately leading to the development of lymphoma.[24] Further research is required to identify modifiable risk factors, susceptible populations, and optimal screening and surveillance modalities.