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Original Research

Breast implant-associated anaplastic large cell lymphoma: A review and assessment of cutaneous manifestations

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ABSTRACT

One newly recognized form of T-cell lymphoma is breast implant-associated anaplastic large cell lymphoma (biALCL), which appears in close proximity to breast implants. The number of reported cases of biALCL is increasing and warrants careful attention by clinicians to more effectively diagnose and treat affected individuals.

As pertinent to dermatologists, the objective of this paper is to present the associated cutaneous features of this clinical entity along with the pathogenesis, management, and clinical outcomes.

biALCL is a T-cell lymphoma in which malignant T-cells are characterized by large pleomorphic and anaplastic morphology and immunoreactivity for CD30, similar to primary cutaneous anaplastic large cell lymphomas (pcALCL). It has a favorable clinical outcome like nonimplant-associated pcALCL and involves the fibrous capsule around the implant, which creates an immunologically privileged site with a peri-implant effusion (seroma). More rare presentations are of a solitary mass.

Appropriate management of biALCL is the complete surgical removal of the implant and total capsulectomy. Dermatologists should be aware of the occurrence of this entity in patients who have breast implants because patients may present specifically for breast-related cutaneous findings or have incidental cutaneous changes noted during a skin examination.

The recognition and timely diagnosis of biALCL is critical to prevent progression to more advanced disease, ensure adequate treatment with removal of the implant, and avoid unnecessary aggressive systemic chemotherapy.

Introduction

Primary breast lymphomas are a rarity and account for approximately 0.04 to 0.5% of all breast cancers (Cohen and Brooks, 1991). The majority of these non-Hodgkin's lymphomas that affect the breast derive from B-lymphocytes and less than 10% are of T-cell origin (Talwalkar et al., 2008). In recent years, a distinct subset of T-cell lymphomas, so-called breast implant-associated anaplastic large cell lymphomas (biALCL), have been described in women with breast implants. Anaplastic large cell lymphomas (ALCL) are a subset of T-cell lymphomas that were first described by Stein et al. (1985) and are characterized by large T-cells with anaplastic morphology and CD30 positive phenotypes.

ALCL consists of a spectrum of diseases that include systemic ALCL and primary cutaneous ALCL (pcALCL; The Non-Hodgkin's Lymphoma Classification Project, 1997). The differential expression of anaplastic lymphoma kinase (ALK) protein in systemic ALCL allows for a delineation of disease prognosis and patient survival. Expression of ALK is a sign of a reciprocal t(2,5) translocation that involves 2p23 and 5q35 chromosomes, which results in the fusion of the ALK gene and nucleophosmin (NPM1; Morris et al., 1994). Tumor cells in the vast majority of systemic ALCL express ALK and an ALK negative expression profile represents a poor prognostic factor that is associated with a more aggressive clinical course (Gascoyne et al., 1999). Among patients with ALK negative systemic ALCL, the 5-year survival rate is 40% while the survival rate of ALK positive systemic ALCL is as high as 80% (Delsol et al., 2001). In contrast to the majority of systemic ALCL, tumor cells in pcALCL are ALK negative. Despite an ALK negative profile, pcALCL has a favorable prognosis with a 5-year survival rate that ranges from 85 to 100% (Woo et al., 2009).

Clinically, pcALCL presents with solitary or multiple red nodules or tumors. Histopathologically, pcALCL is characterized by sheets of diffuse nonepidermotropic infiltrates that are composed of large

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pleomorphic and epithelioid CD30+ T-cells. Histology alone is not sufficient to distinguish pcALCL from its systemic counterpart because the two entities have similar morphologic and phenotypic features (Xing and Feldman, 2015). However, it is critical to distinguish between pcALCL and secondary cutaneous involvement by systemic ALCL because the prognosis and approach to management are different. Whereas pcALCL has a good prognosis and in most cases can be effectively managed with radiation therapy or surgical excision, nodal ALCL requires systemic chemotherapy (Woo et al., 2009). Although the pathogenesis of pcALCL is still not clearly delineated, most speculations with regard to the clonal proliferation of T-cells lies in chronic antigen stimulation, especially in patients with a genetic predisposition (Braverman, 1991).

Breast implant-associated anaplastic large cell lymphoma

Within the spectrum of CD30+ ALCL, a more recently recognized clinical entity is the development of ALCL in association with breast implants (Aladily et al., 2012a, 2012b). Whereas pure ALCL of the breast is a clinical rarity, an increase has been observed in the number of reported cases of biALCL in patients who received silicone or saline breast implants. It has been difficult to quantify the estimated incidence and prevalence of biALCL due to a fairly recent formal recognition and reporting of this entity; however, a case-control study that utilized the national 9 million-patient pathology database was conducted in the Netherlands and established an association between ALCL and breast implants in comparison with patients without an implant, with an estimated odds ratio of 18.2 (95% confidence interval [CI], [2.1-156.8]; de Jong et al., 2008). On the basis of their study, an annual incidence was estimated at 0.1 to 0.3 per 100,000 women with implants (de Jong et al., 2008). Although this estimated incidence is quite uncommon, the steady increase in the number of women who receive breast implants makes it highly pertinent to improve awareness of this clinical entity. In light of concerns over a causal relationship between breast implants and the development of biALCL, the U.S. Food and Drug Administration formally issued a warning for the public in 2011, recognizing a possible link between ALCL and breast implants. Of note, there appears to be no difference in the rate of biALCL occurrence among women who receive implants for breast augmentation versus reconstruction for breast cancer or prophylaxis (Clemens and Miranda, 2015).

Clinical manifestation

biALCL is not a disease of the breast parenchyma. In two-thirds of patients, biALCL presents with a peri-implant effusion (or seroma) and in the remaining one-third as a mass that arises from the fibrous capsule (Kim et al., 2011). In most studies, local swelling was the most common presenting symptom and less frequently, the presenting symptoms included rash, pruritus, pain, erythema, capsular contracture, and pressure (Kim et al., 2011; Xu and Wei, 2014). Some cases have presented with cutaneous findings or had cutaneous involvement concurrently with the seroma and/or mass (Table 1).

To facilitate better recognition of biALCL by dermatologists, we reviewed cases that have been reported in the literature to compile a list (although by no means exhaustive) of possible cutaneous presentations of biALCL (Table 1). A systematic literature review of all reported cases of non-Hodgkin's lymphoma in patients with breast implants was conducted and yielded 29 cases of biALCL (Kim et al., 2011). Of these 29 cases, four patients presented with redness and two patients had other skin manifestations, including one patient who demonstrated an erythematous ulcer and the other subcutaneous nodules (not listed in Table 1; Kim et al., 2011). Of the 127 patients with biALCL that were reported in another study, three patients presented with skin erosions at the time of presentation (not listed in Table 1; Brody et al., 2015). Interestingly, five patients in this analysis had associated concurrent papules that involved the ipsilateral chest and breast. Other noted cutaneous clinical presentations in the literature involved erythematous skin eruptions in five patients prior to the biALCL diagnosis (Table 1; Laurent et al., 2016). In a recent report of a case of biALCL, cutaneous lesions were the primary manifestation of the lymphoma (Table 1; Alcalá et al., 2016). The patient presented with several cutaneous nodules on the right breast and poorly circumscribed, erythematous, indurated papules under the breast (Alcalá et al., 2016).

Lastly, cutaneous T-cell lymphomas (CTCLs) have been reported in the context of breast implants. Duvic et al. (1995) presented cases of mycosis fungoides and Sézary syndrome that were observed in patients with breast implants (Table 1). In another report, a well-described eruption of lymphomatoid papulosis on the chest was noted prior to the diagnosis of biALCL (Aladily et al., 2012a). However, due to the limited number of cases, it is difficult to ascertain whether these were merely coincidental findings or there was a true relationship between breast implants and development of CTCLs in these cases. Since cytological studies have demonstrated that chronic inflammation is a component of biALCL pathogenesis (Kadin et al., 2016), it is now suggested that the pathogenesis of both CTCL and biALCL involve chronic stimulation that often occurs in an immunologically privileged site such as the epidermis (for CTCL) or in the seroma (for biALCL).

Histopathologic features and prognosis

Histopathologically, biALCL is similar to systemic and cutaneous ALCL since it is also characterized by highly pleomorphic T-cells with anaplastic morphology, irregular nuclei, and prominent nucleoli (Xu and Wei, 2014). Mitoses are frequent and there is often a background of inflammatory cells that include small lymphocytes, histiocytes, and eosinophils (Xu and Wei, 2014). Molecular analyses demonstrate T-cell receptor gene rearrangements. Malignant T-cells are CD30+, commonly CD4+, and CD43+, and demonstrate strong B-cell lymphoma 2 immunostaining. However, CD3 and CD2 expression are noted in only 30 to 46% and 30% of cases, respectively (Taylor et al., 2013; Xu and Wei, 2014). Frequently, the expression of CD5, CD7, CD8, and CD15 is also absent (Taylor et al., 2013).

Similar to pcALCL, most reported cases of biALCL have been ALK negative. Although in systemic ALCL a negative ALK status predicts an aggressive clinical behavior, biALCL is similar to pcALCL in that negative ALK predicts an indolent clinical course. In a study that assessed 39 patients with biALCL, 97% had an ALK negative phenotype that was associated with a good prognosis (Story et al., 2013). There have been few reported deaths that were associated with biALCL. However, those patients had nodal and systemic involvement at the time of the diagnosis. Consequently, the survival data appear to suggest a 100% survival rate of patients with localized disease (Story et al., 2013).

Many features of biALCL are akin to what is observed in patients with pcALCL including an ALK negative expression profile, indolent clinical behavior, and response to treatment. With pcALCL, patients often relapse when treated with traditional chemotherapy without an effect on the patient's prognosis (Kempf et al., 2011; Shehan et al., 2004). Similarly, 23% of patients with biALCL had relapses after systemic treatment but this had no influence on the patient's disease outcome (Story et al., 2013).

In patients with biALCL that is associated with an effusion, the tumor cells present within the peri-implant fluid and generally have an indolent course with an excellent prognosis after implant removal and capsulectomy. Patients with biALCL that is associated with a mass usually have concurrent necrosis and sclerosis of the tumor that may result in a multinodular appearance. In these

Table 1
Reported cases of patients with breast implants in close proximity to a T cell lymphoma with concurrent cutaneous manifestations

Diagnosis	Age	Type of Implant	Reason for Implant	Time from Implant to Diagnosis	Cutaneous Symptoms	Treatment	Response to Treatment	Source
SS Stage IVA	38	Silicone	C	3 years	Urticaria in overlying skin that subsided with eventual evolution into generalized exfoliative erythroderma, particularly on upper chest; acral keratoderma	Implant removal, extracorporeal photophoresis and interferon alfa	Responded well with clearing of skin	Duvic et al., 1995
SS Stage IV	48	Silicone	C	3 months	Scaling of palms and soles	Implant removal, capsulectomy	Relatively benign course first 8 years of disease, more resistance after that	Sendagorta and Ledo, 1995
MF Stage IVA	35	Silicone	NA	11 years	Eczematous eruption on breast refractory to steroid treatment with papillomatosis of nipples and symmetric erythematous plaques overlying both breasts	Implant removal, PUVA, eventual Interferon alfa therapy	Death in 1994	Duvic et al., 1995
MF Stage IA	53	Silicone	C	20 years	Enlarged irritated area of skin on left breast evolved into solitary atrophic erythematous plaque 8x13 cm with wrinkled shiny surface	Local radiation	Lesion cleared in 1993	Duvic et al., 1995
biALCL	53	Silicone	R	8 years	Several erythematous cutaneous nodules/papules on the right breast	CHOP chemotherapy and Implant removal	Death from septic shock during treatment	Alcalá et al., 2016
biALCL	56	Silicone	R	13 years	Erythematous skin eruption	Implant removal	No evidence of disease	Laurent et al., 2016
biALCL	54	Silicone	C	3 years	Erythematous skin eruption	Implant removal, CAVP	Death from disease	Laurent et al., 2016
biALCL	74	NA	R	9 years	Erythematous skin eruption	ABDV, radiation therapy (30Gy)	No evidence of disease	Laurent et al., 2016
biALCL	74	Silicone	R	9 years	Erythematous skin eruption	Implant removal, CAVP	No evidence of disease	Laurent et al., 2016
biALCL	58	Silicone	R	7 years	Erythematous skin eruption	CAVP	Death from other cause	Laurent et al., 2016
biALCL	28	Silicone	C	NA	Left mastitis	NA	Alive at 40-month follow-up	Gualco et al., 2009
biALCL	50	Silicone	R	9 years	Nodules	Chemotherapy with CHOP	Initial clinical remission, then relapse	Gaudet et al., 2002
biALCL	72	Silicone	R	32 years	Skin ulcer	Implant removal	NA	Fritzsche et al., 2006
biALCL	60	Silicone	R	4 years	Painful rash	Implant removal	Disease free survival	Aladily et al., 2012a

ABDV, adriamycin, bleomycine, vinblastine, and dacarbazine; biALCL, breast implant-anaplastic large cell lymphoma; C, cosmetic; CAVP, cyclophosphamide, adriamycin, vincristine, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; MF, mycosis fungoides; NA, not available; PUVA, psoralen and ultraviolet A; R, reconstruction; SS, Sézary syndrome; Sx, symptoms.

patients, biALCL has an aggressive clinical course that requires chemotherapy and radiation (Xu and Wei, 2014).

Pathogenesis of biALCL

The pathogenesis of biALCL has not been clearly delineated but several theories have been proposed. Chronic inflammation has been implicated in many different neoplastic processes and in congruence, a study has demonstrated that the lymphocytes of biALCL show features of chronic antigenic stimulation (Kadin et al., 2016). A chronic state of inflammation has been associated with the induction of reactive oxygen species, microRNA instability, and epigenetic changes, which can lead to genetic instability and result in the development and expansion of a malignant clone (Lowe and Storkus, 2011). This proposed mechanism of chronic inflammation-induced lymphoma formation is akin to theories that have been suggested to underlie the development of non-Hodgkin lymphoma that is associated with Sjogren's syndrome, a chronic autoimmune disorder. Similarly, chronic antigenic stimulation and clonal proliferation has been implicated in the development of CTCLs.

A recent hypothesis suggests that silicone rupture or the movement of compounds through the implant's envelope known as silicone bleeding serves as the promulgator for the chronic inflammatory response that ultimately activates antigen-presenting cells (Bizjak et al., 2015). Further, silicone may act as an adjuvant component in the chronic stimulation of T-cells in genetically predisposed patients. This persistent antigenic stimulation of T-cells can ultimately lead to oncogenic mutations that yield lymphomas including CD30-ALCL. Another cause of chronic inflammation in patients with breast implants may be the presence of biofilm-associated organisms including gram-negative bacteria with a propensity for increased T-cell response in humans and implanted pigs (Hu et al., 2015). The reaction to bacterial components that are adherent to the biofilms can also lead to the stimulation of toll-like receptors on immune cells (Bizjak et al., 2015). This is reminiscent of previous studies that suggest that Staphylococcal superantigen endotoxins (SE) may play a role in tumor growth in CTCLs in those that are colonized with SE on the skin and nares (Willerslev-Olsen et al., 2016).

Interestingly, the study that suggested that biofilm-associated organisms were the cause of biALCL also demonstrated that in patients with capsular contracture, the microbiome of tumor samples was significantly different than the microbiome that surrounds nontumor capsular contracture samples (Hu et al., 2015). This latter finding suggests that chronic bacterial biofilm infections may be a contributing factor in the development of biALCL and that different types of bacterial species may cause lymphocyte activation, and proliferation and oncogenic mutations, which ultimately lead to the development of lymphoma (Hu et al., 2015).

A recent study analyzed the cytokine and transcription factor expression profile of biALCL tumor cells and demonstrated that malignant T-cells are derived from Th1/Th17 cells, which supports the hypothesis that chronic bacterial and antigenic stimulation of T-cells may play a role in the expansion of a T-cell clone, which eventually leads to the development of a lymphoproliferative disorder

(Kadin et al., 2016). This is analogous to a chronic *Helicobacter pylori* infection, which has been associated with gastric mucosa-associated lymphoid tissue (MALT) lymphoma (Wang et al., 2013).

Although further research is required to precisely delineate the mechanism of lymphomagenesis, a recent study harvested cells from the peri-implant fluid of a patient with biALCL to achieve this goal (Thompson et al., 2010). Researchers have established the T-cell lymphoma breast 1 cell line, which closely mimics the disease, with the hopes of characterizing the development of this clinical entity (Thompson et al., 2010). Since biALCL has a clinical behavior that closely resembles pcALCL, research into the biALCL pathogenesis will definitely increase existing knowledge with regard to pcALCL as well.

Work-up and management

Dermatologists are more involved in the diagnosis of biALCL with cutaneous features than its treatment. Skin biopsies should have immunoperoxidase studies to include all T-cell markers along with CD30 and ALK. T-cell clonal expansions should be tested for from skin biopsies with polymerase chain reactions. Imaging with positron emission and computed tomography scans is routine to evaluate potential lymph node involvement. Hematologic studies with flow cytometry for CD3, CD4, and CD8 are the initial screen for peripheral blood involvement. An ultrasound of the breasts should be performed to look for effusion. Since the surgical removal of breast implants and associated capsules are the cornerstone of therapy, referral to a surgical specialist should be timely with all imaging studies completed. Oncology referrals will assist in the determination of the need for systemic therapies although the current therapy of localized disease is surgery followed by watchful waiting.

Discussion

Although the majority of reported cases of biALCL have had a clinical presentation that is consistent with seromas or a mass, there have been cases that presented with cutaneous findings or had cutaneous involvement concurrently with the seroma and/or mass (Table 1). Since patients may not always be attentive to breast-related changes, dermatologists should consider this entity in the differential diagnosis of women who have implants. The recognition of biALCL in patients with breast implants is particularly important for dermatologists because they may be the first among clinicians to see patients when they present with cutaneous changes that involve the breast. In most cases, biALCL has an excellent prognosis but progression to systemic disease may occur.

Conclusion

The objective of this paper is to raise awareness among dermatologists and dermatopathologists of T-cell lymphomas that have occurred in association with breast implants, with a particular emphasis on the newly recognized rare clinical entity known as biALCL. Although biALCL primarily presents with an effusion that is confined to the peri-implant region or with a mass and/or tumor, this disease can present with cutaneous lesions either prior to other signs or concurrently with the primary manifestations. For this reason, dermatologists should be aware of the occurrence of this entity among patients with breast implants and have a high index of suspicion when evaluating these patients.

Epilogue about Dr. Jane Grant-Kels

Jane has been an exceptional leader and mentor in so many areas that her accomplishments and contributions are near impossible to list. If I still needed to highlight one of her special strengths, I think she is just the very best at encouraging and supporting everyone around her to pursue their career goals, taking a unique interest in nurturing our talents. Jane has been stimulating all of us to think big, push the envelope, and reach for our highest potential. She has been crucial in my case, for example, not just to be recruited for my current position but also to ensure that I have the right mix of exposures and tasks. Much like a mother figure, she has gently supported and promoted me throughout the years for me to achieve my potential. In addition, Jane has been incredibly supportive in helping me pursue my special interests in cutaneous lymphomas, offering me unique opportunities to establish collaborations, recommending me for workshops and presentations, and connecting me with an array of experts in the field including my dear mentor, Dr. Peter Heald. Jane has touched so many lives and I have been so incredibly lucky that my life is one of those.

Kati Ferenczi

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