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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

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