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Anaplastic Large Cell Lymphoma In A Patient With Breast Implant (BIA-ALCL): An Extensive Review

Mahpara Nawazish, Sana Iqbal, Irfan Saeed, Ubaid Ur Rehman

IMPORTANCE Breast implant associated with anaplastic large cell lymphoma (BIA-ALCL) is a newly diagnosed non-Hodgkin lymphoma. This is a variant of T cell lymphoma and a rare disease but its increasing use in patients with breast implants after mastectomy makes it more challenging for the whole of the world. The exact pathogenesis has not been explained so far. It generally appears as a unilateral effusion limited to the capsule of textured implants. BIA-ALCL tends to form a mass that spreads regionally through the capsule into surrounding tissues and then from soft tissues to lymph nodes. Unlike other non-Hodgkin lymphomas, in BIA ALCL surgery is a mainstay of the treatment and it includes removal of capsule and implant at an early stage (stage I and II). For advanced stages, III and IV, adjuvant therapy including chemotherapy, radiation therapy, and brentuximab vedotin is used. The basic theme and aim of our review article are to provide precise information available on BIA- ALCL including its prevalence, pathogenesis, clinical findings, imaging, an algorithm for treatment, and recent international recommendations on BIA-ALCL. By this review, we want to increase the understanding and bring awareness to the practitioner's community about BIA-ALCL.

KEYWORDS Breast implant-associated anaplastic large cell lymphoma, breast implants, lymphoma

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Anaplastic large cell lymphoma (ALCL) is usually CD30 positive and is a type of T-cell non-Hodgkin lymphoma. They are subdivided based on anaplastic lymphoma kinase (ALK) ALK-positive and ALK-negative and primary cutaneous ALCL which have the same histology but divided into different clinical groups.[1] Breast implants are divided into three categories. Firstly based on components such as saline and silicone gel-filled, secondly on the surface (textured surface and smooth surface), and thirdly on configuration into symmetric and non-symmetric.[2] Worldwide, almost 1.5 million women underwent breast implants surgery every year, out of which nearly 4.5 million implants were done in the United States of America. The main purpose of breast implants is to augment and reconstruct the breast in patients following mastectomy.[2] "The first case of BIA-ALCL was reported by Keech and Creech in 1997", and studies revealed that BIA-ALCL has a strong association with a textured type of implants. The exact mechanism is still unclear.[3] [4] In 2008, a Dutch study reported a positive link between BIA ALCL and breast implants by using its vast data collected from different countries on pathology, that described various forms of breast pathologies.[3,5] When classic systemic ALCL and BIA ALCL compared; there were two pathological types recognized. One is the seroma type that was most common and the second was the mass type that was less common but aggressive in nature.[6] In the early postoperative period, the chief complaint is effusion around the implant and can be associated with sepsis, non-specific inflammatory reaction, and hematoma formation. The presence of effusion more than 1 year after implant surgery is uncommon, approximated to be less than 1 %. Any deferred "seroma" formation should raise the doubt of BIA ALCL. [7]

EPIDEMIOLOGY

"The first case of ALCL in a patient with breast implant was reported by Keech and Creech in 1997". [3] Of all extranodal Non-Hodgkins lymphoma [NHL] Only 1% are non-Hodgkin's lymphomas of the breast and 0.7 % of all breast cancers.[8] B-cell lymphoma are most common NHL but T cell variant is found in 10%.[7] Post breast implantation, patients can present with the symptoms of BIA ALCL after a minimum of 3 months to a maximum of 25 years.[8]

PATHOPHYSIOLOGY

The mechanism of BIA-ALCL remains uncertain. In the literature, three theories have been proposed, based on antigen stimulation response, bacterial biofilm, and JAK/STAT pathway.[9] According to the first theory, textured

implants have more surface area which incorporates more bacteria that induces inflammatory response through macrophages, interleukins II and VI and T type cells stimulation which leads to antigens stimulation response, inflammation, immune response, and cell proliferation that alters the genetic makeup and ultimately the formation of lymphoma.[9] Second theory postulated that early investigations identified a gram-negative bacillus, Ralstonia pickettii, in establishing a subclinical, peri-prosthetic biofilm, leading to a lipopolysaccharide (LPS) endotoxin-induced carcinogenesis. After a more careful examination, the Ralstonia data have since been refuted, and currently, no clear association between the breast microbiome and BIA-ALCL pathogenesis exists.[10] The third theory suggests that the presence of an uncommon activating variant of JAK3 (V722I)may have provided a hereditary inclination. However, the joint JAK1/JAK3 mutations are very much indicative of co-occurrence of acquired mutations in STAT 3 and JAK 1 in the same tumor in patients with ALK-negative systemic ALCL, which showed its selective advantage of a synergistic effect of combined mutations. Further concentrates for a huge scope expected to decide the frequency of JAK1/STAT3 transformations in BIA-ALCL as well as genetically predisposing factors.[11]

CLINICAL FEATURES

Around 96% of the patients present with local symptoms such as pain, redness, alteration in the shape as well as size, lymphadenopathy, and breast skin lesions. While only 9% of the patients present with systemic symptoms like fever, night sweating, weight loss, and non-breast skin lesions. Most patients came with a presentation of seroma and 15% with breast masses. Majority of the patients present with unilateral involvement and only a few patients present with bilateral BIA ALCL.[12] The mean time interval of developing breast lymphoma is almost 10 years after breast implantation following mastectomy. Seroma formation is found in around 60% of patients, while with a mass the ratio is 17% and combined seroma and mass presentation are found in 20% of the population.[13] Factor that increases the risk of developing BIA ALCL are obesity, genetics, and history of autoimmune disease, certain races, or ALCL in other sites.[14]

HISTOLOGICAL FEATURES

On histology of seroma, malignant cells are appreciated on cytology and cell block preparation. After capsulectomy, mostly tumor cells are aligned at the luminal side of the fibrous capsule, entrapped in the fibrinoid network, which can vary in distribution patchy or focal distribution. In patients presenting with the mass lesion, the malignant cells appear in the form of bundles and sheets mixed with eosinophils along with necrosis and sclerosis.[15] Tumor cells are variable in size and shape, having a high mitotic count with hallmark cells that are common in all types of ALCL. The cells may some of the time have eccentric bean-shaped nuclei, multinucleated, and look like Reed–Sternberg cells.[16] The diagnostic board should incorporate B cell markers (CD20, CD79, PAX5) and EBV to prohibit other huge cell lymphomas [diffuse huge B cell lymphoma (DLBCL) and classical Hodgkin lymphoma (cHL)]. A pan-cytokeratin to rule out poorly differentiated carcinoma, and S100 and Melan-A to eliminate melanoma, are additionally fundamental in this setting.[16] "They are strongly positive for CD30, sometimes for CD43, often positive for the cytotoxic markers TIA-1, granzyme B, and perforin Tumor cells are negative for Epstein-Barr virus (EBV) and ALK".[15]

IMAGING STUDIES

Imaging studies of BIA-ALCL may show an effusion and mass. "Adrada et al studied the sensitivity and specificity of different imaging modalities used for detection and differentiation of BIA-ALCL".[17,7] The ultrasound was considered a gold standard test in the detection of seroma which was 84% sensitive, and 75% specific. Magnetic resonance imaging (MRI) had 82% and 50% sensitivity and specificity respectively for effusions. PET/ CT was the most commonly used modality to detect tumor mass. Another useful screening modality for breast carcinoma is mammography, and had poor sensitivity for effusion detection around a breast implant, at about 30%.[17]

DIAGNOSIS

Tools that are helpful for diagnosis of BIA-ALCL include a detailed history, physical examination, imaging[ultrasonography, Magnetic resonance imaging(MRI), Positron emission tomography(PET)/Computerized tomography (CT)] and biopsy for cases with breast or axillary masses and nodal metastasis. To rule out BIA-ALCL aspiration of 50 to 1000 mL is advised. Send aspirate for further evaluation (culture and sensitivity, flow cytometry, and immunohistotyping for CD30 and other T cell markers) flow cytometry, and immunohistochemistry. For indeterminate cases, follow-up after every 3 to 4 months is recommended. PET/CT helps to describe the spread of lymphoma in patients with lymph nodes involvement.[2]

PREOPERATIVE EVALUATION/STAGING

For BIA-ALCL, two systems of staging are used. One is the TNM staging system and the other is the Lugano modification of the Ann Arbor staging system. Later was previously been used for non-Hodgkin lymphoma. In this system, stage IE disease is limited to the breast or implant capsule, In this stage, IIE disease is spread to or involves local lymph nodes.[2] Most patients have early-stage disease, that

is stage IE (83%–84%) or stage IIE (10%–16%), while a few of them (0%–7%) fall into stage IV disease with this system. The major drawback of the Ann Arbor staging system is that it does not describe capsular invasion. Now the TNM staging system modeled is currently used for BIA ALCL staging after the American. However, the "TNM classification describes BIA-ALCL as a spectrum of disease from stage IA (35%–70%, effusion only), IB (3%–11%), IC (8%–13%), IIA (8%–25%), IIB (3%–5%), and III (3%–9%) to IV (1%–2%)".[18] This staging system is much more oppressive in terms of event-free survival and more precisely depicts overall survival in contrast to Ann Arbor classification, and is therefore suggested now a days.[16]

TNM Staging System

T: Tumor Extent	
T1	Limited To Effusion Or Luminal Side Of Capsule
T2	Early Capsular Invasion
T3	Cell Sheets Infiltrating The Capsule
T4	Lymphoma Spread Beyond The Capsule
N: Nodal Extent	
N0	No Involvements Of Nodes
N1	One Local Lymph Node Involvement
N2	Various Local Lymph Nodes Involvement
M: Metastasis	
M0	No Distant Spread
M1	Spread To Different Organs
STAGES	
A	T1N0M0
IB	T2N0M0
IC	T3N0M0
IIA	T4N0M0
IIB	T1-3N1M0
III	T4N1-2M0
IV	Tanynanym1

TREATMENT

Surgical Management: The management is based on early diagnosis, complete excision, and removal of the mass and the adjoining area involving the capsule of the implant is the basic step. Radical mastectomy has no significant role in the management of BIA-ALCL because this is not a pathology of breast tissue. In more than 80% of the patients, the disease is localized to the capsule so only Surgical removal is effective.[1,10] Biopsy of lymph nodes that are enlarged pathologically may be required at the time of surgical resection. The recurrence of BIA-ALCL does not appear to be lessened even after full axillary nodes dissection. About 4.6% of patients have had bilateral capsular involvement, removal of the textured type breast implant on the contralateral side is also suggested.[3] A flap surgery is a new convenient and emerging method in which a type of tissue is taken from the donor site and attached to the recipient site with intact blood circulation. An analogous fat grafting is another useful method for cosmetic purposes.[3] The implant capsule should be removed completely since the remains of the scar capsule increase the risk of disease recurrence. The role of adjuvant therapies like radiations is important in case of incomplete resection. For a localized disease that is not disseminated, complete removal by surgery gives good results with the majority of patients remaining disease-free for a longer duration.

Adjuvant Therapy: Adjuvant therapy (radiotherapy, chemotherapy, and brentuximab vedotin) are useful for patients with incomplete resection, local recurrence, and nodal metastasis.[1] Localized radiation (24-36 Gy) followed by surgery is helpful in patients with a localized disease where complete excision is not possible.[1,19]

Survival Rate: Prognosis of breast implant ALCL is better when contrasted with systemic ALCL.[17, 14] when a tumor is confined to the capsule the prognosis is good as compared to the tumor that invades the capsule and surrounding tissues. Specialists strongly oppose that the prognosis is worse in patients who have a history of breast tumor or lymphoma.[14]

DISCUSSION

The World Health Organization (WHO) categorized BIA ALCL and described guidelines for management in 2016.[18] Breast augmentation and implantation surgery has been increasingly used over the world since the first augmentation procedure done in 1962.[18] Low frequency of this infection itself, assessed at 0.1 per 1 lac population every year, makes it particularly hard to predict the link between lymphoma and breast implants.[20] Various triggers have a role in the development of BIA ALCL, including mechanical grafting, implant materials leaking into invading tissue, and bacterial growth. In option, an intensive appraisal of the effect of JAK1/STAT3 pathway changes may provide extra understanding in the mechanism of BIA ALCL, just as immediate helpful procedures for its treatment. Progressing and future examination on the atomic components basic BIA-ALCL may give better choices to its anticipation and treatment in all patients.[21] Now treatment with brentuximab vedotin which is an antibody-drug conjugated to a chimeric CD30 gives excellent results and considers the first line of treatment. Since 2011, the FDA has found a way few ways to all the more likely comprehend this issue, incorporating a top to a bottom survey of post-approval study information,

medical reports, logical writing, breast implants associated registries, and public conversations. In March 2019, the FDA examined many breast implants related concerns and worries in a public warning board of trustees meeting.[22] In October 2019, the FDA delivered a draft direction submitting various proposals to help women approach breast implants advantage and hazard data.[22] The FDA has prompted medical services suppliers and embed makers to report affirmed instances of iALCL through "Med Watch: The FDA safety information and adverse event reporting program.[23] In July 2019, the FDA-refreshed information base announced 573 instances of BIA-ALCS, with 116 new cases and 24 new deaths worldwide since the past correspondence in March 2019 and suggested a deliberate review of Bio cell items in the USA.[23] Doctors ought to be urged to report their involvement in brentuximab vedotin for BIA-ALCL to a repository like the PROFILE (patient registry and result for breast inserts and anaplastic large cell lymphoma etiology and the study of disease transmission) vault to permit alteration of proof-based rules for this phenomenal illness.[23]

CONCLUSION

BIA-ALCL is an unusual category of CD30- positive. T cell type lymphoma is usually developed with a textured type of breast implant almost ten years after its implantation. The diagnostic modality of choice to evaluate a delayed onset seroma is ultrasound. Surgical excision should consider in all cases. Recent studies identified aberrant JAK STAT3 pathway involvement which may serve as a therapeutic target for JAK-STAT inhibitors in the future. The revelation of BIA-ALCL presented significant and clinical worries that ought to be incorporated in the consideration interaction for a lady that chooses to go through breast implantation. Consequently, it is important to design a bunch of shrewd suggestions for oncologists and patients meant to build information about the danger and the medicines accessible. An absence of itemized data may prompt negative feelings lessening imperfect choices and diminishing consistency with the consideration. All nations and government organizations ought to advance mindfulness bringing campaigns up in request to sharpen the doctors for a legitimate cognizance of this novel illness element. To the end, more studies are needed to further delineate the most effective therapeutic regimens in the case of disseminated disease.

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