



Comprehensive Evaluation of the Current Knowledge on Breast Implant Associated-Anaplastic Large Cell Lymphoma

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Arch Plast Surg 2022;49:141–149.

Abstract

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a recently spotlighted T-cell origin non-Hodgkin's lymphoma with an increasing incidence of over 800 cases and 33 deaths reported worldwide. Development of BIA-ALCL is likely a complex process involving many factors, such as the textured implant surface, bacterial biofilm growth, immune response, and patient genetics. As the incidence of BIA-ALCL is expected to increase, it is important for all surgeons and physicians to be aware of this disease entity and acquire thorough knowledge of current evidence-based guidelines and recommendations. Early detection, accurate diagnosis, and appropriate treatment are the foundations of current care.

Keywords

- ▶ BIA-ALCL
- ▶ breast implants
- ▶ biofilm
- ▶ immunity
- ▶ genetics

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a recently spotlighted T-cell origin non-Hodgkin's lymphoma. Although the majority are localized with favorable prognosis that they can be effectively cured by surgical explantation of the breast implants with capsulectomy, a small percentage of cases experiences widespread dissemination and recurrence, which requires systemic therapies. To date, over 800 cases and 33 deaths have been reported worldwide.¹ Despite its low incidence, BIA-ALCL is one the greatest compelling medical challenges in plastic surgery today due to the increasing application of breast silicone implants for aesthetic and reconstructive indications. Early detection, accurate diagnosis, and appropriate treatment are the foundations of current care.

The first case of BIA-ALCL worldwide was reported in 1997,² and a growing number of related literature have been pub-

lished since.^{3–7} It was recognized as a distinct clinical entity of ALCL by the World Health Organization in 2016 and recognized by the U.S. Food and Drug Administration more recently.^{8,9}

Korea is no longer safe from the risk of BIA-ALCL. The first case in Korea was reported in 2021.¹⁰ A 44-year-old woman with a history of breast augmentation with textured implants for cosmetic purpose presented with a late-onset peri-implant effusion and a CD30+ ALK– histology. Abundant CD30+ cell infiltration was observed in pathology, and activation of the JAK/STAT3 pathway and strong PD-L1 expression was found in the RNA sequencing. Also, unlike the Caucasian BIA-ALCL molecular profile, which is characterized by activated CD4+ memory T cells, the molecular profile of the lymphoma was characterized by a CD8+ T-cell phenotype. So far, there have been three cases of BIA-ALCL in Korea, but no death has reported yet.¹¹

DOI <https://doi.org/10.1055/s-0042-1744422>.
ISSN 2234-6163.

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Epidemiology

The total number of BIA-ALCL cases reported continues to increase with over 800 cases and 33 deaths worldwide, confirmed by the Patient Registry and Outcomes for breast Implants and anaplastic large cell Lymphoma Etiology and Epidemiology (PROFILE) Registry, a joint collaboration between the American Society of Plastic Surgeons (ASPS), Plastic Surgery Foundation (PSF), and Food and Drug Administration (FDA).¹²⁻¹⁵ This may be largely due to the recently increased awareness of the disease.

The reported incidence of BIA-ALCL varies greatly depending on the implant texture or geographic variation.¹⁶⁻¹⁹ In a prospective study of 17,656 patients with 31,985 textured breast implants, 8 cases were reported with an incidence of 1 in 4,424 prostheses or 1 in 2,207 patients.²⁰ However, the risk was much lower in less textured implants with an incidence of only 1 in 50,000 to 80,000 cases.²¹⁻²³ In 2020, the U.S. FDA reported 573 cases of BIA-ALCL, including 385 cases with a history of textured implants, 162 not specified, and 26 with smooth implants.²⁴ However, the 26 cases with smooth implants had either a history of prior exposure to textured implants or no clinical history to review. As a result, many references today say that there are no confirmed cases of BIA-ALCL with only a smooth implant clinical history.

There may be also a geographical variation, with the BIA-ALCL incidence being 1 in 11,765 (255 cases) in the United States, 1 in 6,920 (40 cases) in the Netherlands, and 1 in 3,345 (81 cases) in Australia.²¹⁻²³ According to the Australian Therapeutic Goods Administration (TGA), the estimated lifetime prevalence of BIA-ALCL is 1 in 2,500 to 25,000 patients with a textured breast implant, while the estimated average risk in the United States is 1 in 30,000 patients with a textured device.¹² Currently, the highest reported incidence of BIA-ALCL is in Australia and New Zealand where systematic registry systems have been established in early times, whereas it has been found to be extremely rare in Asian, African, and Native Americans.¹⁴ Such differences in incidence may result not only from the genetic variability between different races but also from less awareness of the disease and relatively delayed organization of registries in Asian countries.

History of Textured Breast Implants and Current Issues

There are two main types of breast implants: smooth surfaced and textured. Textured surface adheres to the fibrous capsule and helps maintain implant position and orientation for anatomically shaped implants. The first textured implant was introduced in 1968, known as a "Natural Y," which included a 1.2- to 2-mm-thick polyurethane foam coating on the outer surface of the implant. Their use increased significantly in the 1990s because these implants were known to help prevent capsular contracture.^{8,25,26} Several alternative technologies in surface texturing were introduced to mimic the polyurethane surface texture, and there are three main techniques to generate the surface texture of

silicone implant shell, which are the salt loss, gas diffusion, and imprinting techniques.²⁷

The application of textured breast implants for cosmetic and reconstructive purposes is increasing with current estimates suggesting over 35 million textured breast implants worldwide.^{19,28,29} The United States have the highest prevalence of BIA-ALCL with ~70,000 textured breast implants inserted per year.³⁰ In Europe and Australia, the textured implants account for nearly 90% of device preference.³¹ Meanwhile, Korea is becoming a country with the third highest number of cosmetic breast procedures following the United States and Brazil. In all, 213,000 textured implants have been implanted in Korea since the approval of textured devices in 2007.¹⁰

In 2017, the significant risk of textured implants in developing breast-ALCL was first reported, with an incidence of 2.03 in 1 million patients in a year, which was 67 times greater than that of the primary ALCL.¹⁶ Many other studies have been reported to support that the development of BIA-ALCL is exclusively associated with the texture of implants.²⁰⁻²³ The textured implants are known to develop up to 72 times higher load of bacterial biofilm on the implant surface as compared with smooth implants due to their increased surface area.³²⁻³⁴ Also, the immune response with greater preponderance of T-cell lymphocytes, rather than B cells, is more abundant and active with textured than smooth breast implants.³⁵ The risk is even higher in more robustly textured or polyurethane-covered implants. A prospective study reported that 4 of 17,656 patients with Allergan-textured implants developed BIA-ALCL.³⁶ The "salt-loss" manufacturing technique of Allergan creates an exceptionally coarse textured surface, which causes the highest risk of BIA-ALCL with an estimated incidence of 1 in 355 to 2,207 patients.³⁷

Currently, there are millions of patients with textured breast implants worldwide, which poses a significant risk for them exposed to the possibility of BIA-ALCL development. In 2019, the French National Agency for the Safety of Medicines and Health Products restricted the sales of macro-textured surface breast implants.³⁸ In the same year, the Canadian Health Department advised suspension of license for textured implants as a precautionary measure.³⁹ Furthermore, the FDA requested that Allergan recall its textured breast implants and tissue expanders from the global market.⁴⁰

Pathogenesis

Development of BIA-ALCL is likely a complex process involving many factors, such as the bacterial biofilm growth, immune response, and patient genetics.

Bacteria Biofilm

One of the leading theories of pathogenesis includes the gram-negative bacteria, mainly *Ralstonia pickettii*, infiltrating the biofilm on the surface of textured implants resulting in lymphocyte stimulation (► Fig. 1).³² In vitro and in vivo models showed significantly higher loads of bacteria attached to textured implants than to smooth implants

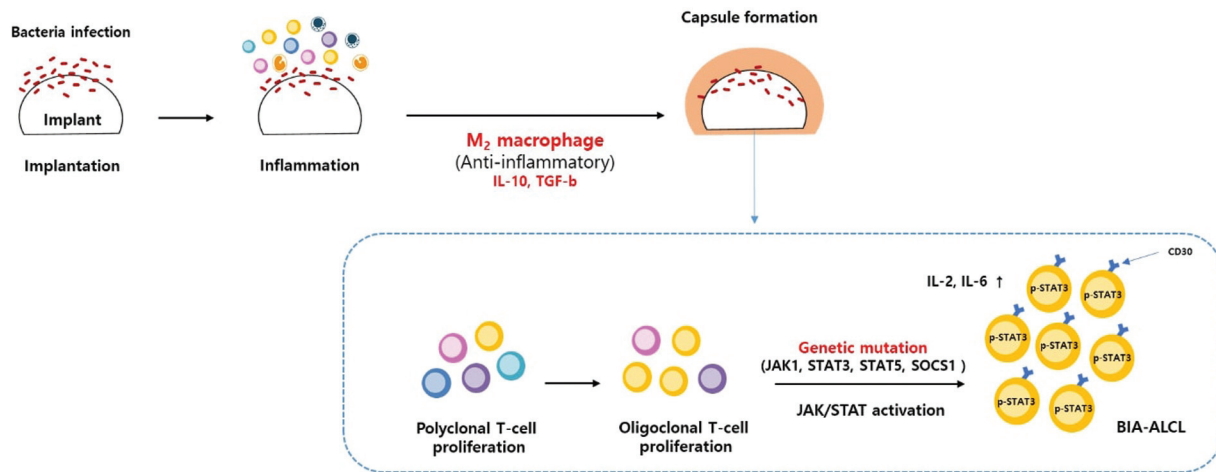


Fig. 1 Pathophysiological mechanism of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL).

($p < 0.001$ and 0.006 , respectively), supporting subclinical infection as a trigger factor.^{17,41}

The tissue grows into the surface of the textured implants and stimulates the antigenic trigger of innate immunity. This induces T-cell proliferation and prolongs chronic inflammation.⁴² A study of 57 implants removed due to capsular contracture showed that all of them had biofilms.²³ The number of lymphocytes showed significant association with the number of bacteria detected, which included significantly more T cells than B cells ($p < 0.001$). CD4 T cells were the predominate cell type.^{43,44} Chronic inflammation from indolent infections leads to malignant transformation of T cells that are anaplastic lymphoma kinase (ALK) negative and CD30 positive.

Immunoglobulin E-Mediated Allergy

Some patients show an allergic profile of cytokines mediated by immunoglobulin E (IgE). In 2018, the cell lines of BIA-ALCL were found to produce IL-13, a signature cytokine of allergic inflammation.⁴⁵ Also, the cells were often surrounded by mast cells and eosinophils, a feature generally absent in the systemic ALCL. IgE was attached at the surface of mast cells and follicular dendritic cells in capsules and regional lymph nodes of anaplastic lymphoma, and the plasma cells were identified as a possible source of IgE. These findings all suggest the possibility that an amplified immune response with respect to chronic allergic reaction might underlie the pathogenesis of BIA-ALCL.

Genetic Predisposition

Genetics is also thought to be a major risk factor for the disease. Some BIA-ALCL patients have somatic mutations in the JAK/STAT signaling pathway as well in SOCS1, TP53, and DNMT3A.⁴⁶ A recent study showed that BIA-ALCL is frequently characterized by JAK/STAT-activating mutations, also identifying recurrent mutations of epigenetic modifiers in more than 70% of cases.⁴⁷ BIA-ALCL cells are known to upregulate genes for cell motility, such as chemokine receptor 6 and chemokine ligand 14, and other genes including peroxisome proliferator-activated receptor gamma (PPARγ)

and Janus kinase 2 (JAK2), as compared with other peripheral T-cell lymphomas.⁴⁸

ALCL Induced by other Prosthesis

Cases of CD30-positive, ALK-negative ALCL associated with any type of prosthesis other than breast implants, such as dental, gluteal, and silicone-containing port device implants, are not rare.^{49–53} Although the mechanism of mechanical friction have been suggested as the leading theory of pathogenesis of ALCL, the evidence remains limited.⁵⁴

In 2017, a case of ALCL occurred at the adjustable gastric band insertion site for bariatric surgery.⁵⁰ The prosthesis was fabricated with silicone-based elastopolymer, similar to breast implants. The leading developmental theory is chronic inflammatory response and bacterial biofilm infection of the implant surface. In 2020, another case was reported in the stainless steel plate and screws used for reduction of a tibial fracture.⁵⁵ The debris of metallic orthopaedic implant might be capable of causing significant damage to the macrophages, which can cause immunogenic response to increase T- and B-cell proliferation.

Evaluation and Classification

Clinical Manifestation

The mean time to clinical presentation is ~10 years after implant placement.⁵⁶ The most common clinical presentation is a late peri-implant effusion with breast enlargement (→ Figs. 2 and 3).⁵⁶ Almost 80% of patients are initially seen with a delayed seroma, 8% with an observable mass, 7% with both a mass and seroma, and 18% with other entities, such as capsular contracture, skin lesions, and axillary lymphadenopathy. Rarely, B-symptoms can also occur, including fever, lymphadenopathy, night sweats, and fatigue.^{57–59} The estimated risk of BIA-ALCL is up to 10% in patients with delayed seromas.⁶⁰

Diagnostic Workup

The National Comprehensive Cancer Network (NCCN) guidelines for the diagnosis and treatment of BIA-ALCL were

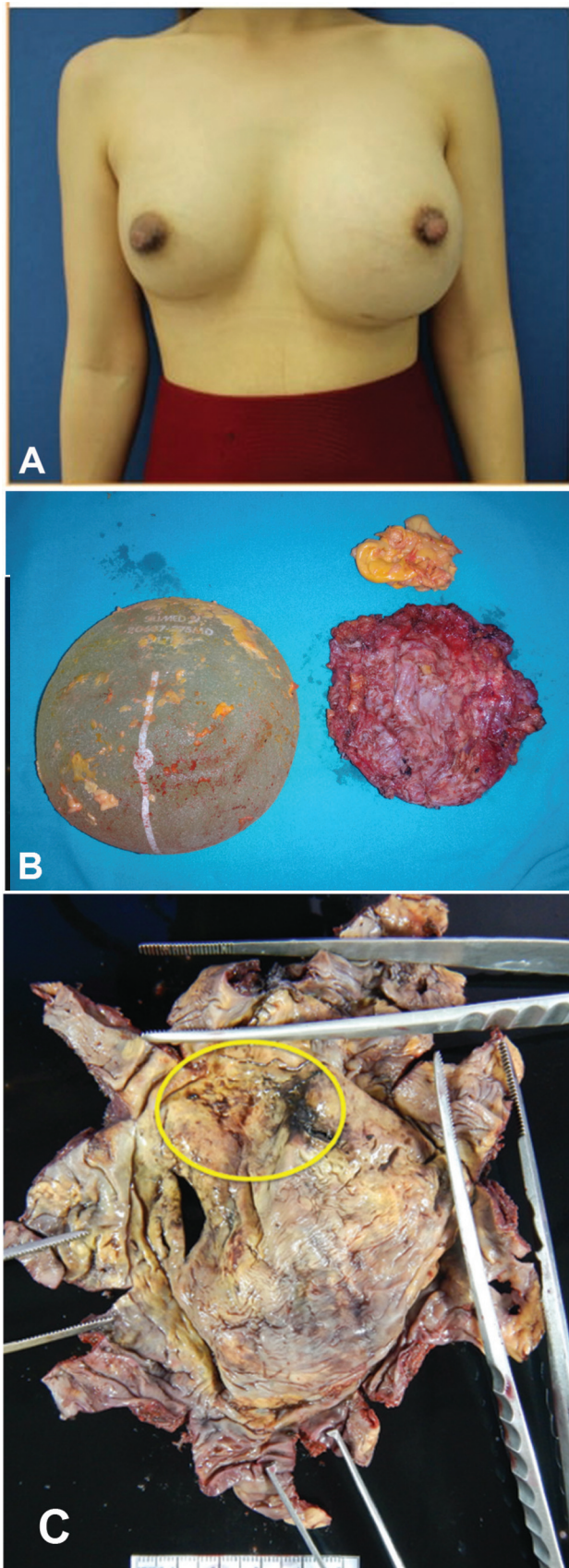


Fig. 2 (A) Clinical presentation of breast enlargement with peri-implant effusion. (B, C) Removed textured implant and irregularly surfaced implant capsule. (Source: Reprinted with permission from Thienpaitoon P et al⁵⁶)

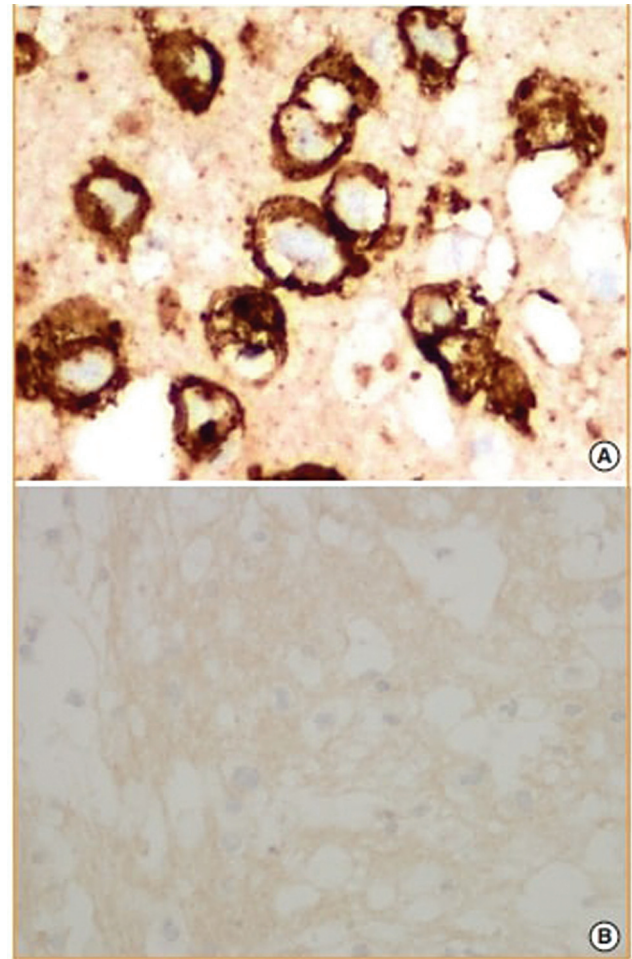


Fig. 3 (A, B) Immunohistochemistry stain of CD30 and ALK.

established based on the current understanding of the literature.⁶¹ Ultrasound is usually the first choice of study in the evaluation of patients with breast swelling and can be used for image-guided fine-needle aspiration of fluid. It is known to convey an 84% sensitivity and a 75% specificity for detecting an effusion and 46% sensitivity and 100% specificity for detecting a mass.⁶²

The aspirated peri-implant fluid often appears thick and cloudy on the gross appearance. It is sent for cytology and flow cytometry, including evaluation of the CD30 expression. When acquiring the fluid, it is important to obtain a large volume of at least 50 mL to prevent indeterminate results.⁶³ The cytology shows large pleomorphic lymphocytes with abundant cytoplasm and an eccentric, kidney-shaped nucleus with prominent nucleolus.⁶⁴

Immunohistochemistry is used to confirm the diagnosis of BIA-ALCL, which involves CD30 positive and ALK negative. CD30 is expressed on activated B cells and T cells. Epithelial membrane antigen is overexpressed in several cancers, including breast cancer, and ALK is a fusion gene present in up to 70% of systemic ALCL. T-cell antigen expression is variable, with the most frequently expressed markers being CD4, CD3, CD45, and CD2, in decreasing order. Molecular analysis shows monoclonal T-cell receptor (TCR) γ gene rearrangement.

Table 1 TNM stage classification of BIA-ALCL (2019 NCCN guidelines)

TNM classification		TNM stage	
T: Tumor extent		IA	T1 N0 M0
T1	Confined to effusion or a layer on luminal side of capsule	IB	T2 N0 M0
T2	Early capsule infiltration	IC	T3 N0 M0
T3	Cell aggregates or sheets infiltrating the capsule	IIA	T4 N0 M0
T4	Lymphoma infiltrates beyond the capsule	IIB	T1–T3 N1 M0
N: Lymph node		III	T4 N1–N2 M0
N0	No lymph node involvement	IV	Tany Nany M1
N1	One regional lymph node (+)		
N2	Multiple regional lymph nodes (+)		
M: Metastasis			
M0	No distant spread		
M1	Spread to other organs/distant sites		

The thin and discontinuous tumor cell layer on the surrounding capsule can lead to a false-negative result by capsule histology. Also, in less aggressive cases, the tumor cell is usually confined only in the inner capsule. When a mass is present, the cells often exhibit a sheetlike growth, giving a multinodular appearance with areas of geographic necrosis and sclerosis.

Other routine laboratory works should include complete blood cell count with differential count, comprehensive metabolic panel, and lactate dehydrogenase level. For staging, positron emission tomography and computed tomography are the preferred imaging modalities to assess for systemic evaluation and are most frequently performed after surgery to allow adequate time for postsurgical wound healing and to minimize the risk of false-positive [18F]-fluorodeoxyglucose avidity.

Staging

The TNM staging, which is typically used for solid tumors, is suggested for BIA-ALCL rather than the Ann Arbor staging classification that is used for lymphoma.^{65,66} Using the Lugano revision of the Ann Arbor Staging System, most patients have early-stage disease (83% stage IE; 10–16% stage IIE).⁶⁷ A validated BIA-ALCL-specific TNM staging system has been encouraged by the NCCN because stage I patients are well curable with surgery alone.

Patients in stage I have lymphoma that are confined to effusion or in the luminal side of capsule without penetration beyond the capsule (▶ **Table 1**). Stage IIA has lesions limited to the breast but have invasion beyond the capsule into surrounding tissues. Stage IIB has involvement of a single regional lymph node. Stage III is the combination of stage IIA and IIB, and stage IV is considered when distant involvement of sites other than ipsilateral breast and regional lymph nodes is present. Liver, small bowel, central nervous system, and bone involvements have been reported. Disease-related death most commonly occurs following invasion into the chest wall and the mediastinum.^{60,62,68}

Immunophenotypes: ALK+ / ALK– / Primary Cutaneous ALCL / BIA-ALCL

The 2017 World Health Organization (WHO) lymphoma classification established four different entities of ALCL, characterized by different pathogenesis and clinical presentations. These four categories include the ALK+ ALCL, ALK– ALCL, primary cutaneous ALCL, and BI-ALCL, which has recently been incorporated as a new provisional entity.⁸

ALK+ ALCL is a peripheral T-cell lymphoma defined by the rearrangement of ALK gene resulting in expression of ALK protein. Proliferation of cells with eccentric kidney-shaped nuclei is commonly present as in BIA-ALCL.⁶⁹ The activation of chimeric ALK fusion protein promotes the development of ALK+ ALCL through several signaling pathways, such as JAK/STAT, receptor tyrosine kinase-extracellular signal-regulated kinase (RAS/ERK), and phosphoinositide-3-kinase–protein kinase B (PI3K)/Akt pathways.⁷⁰ The presence of ALK+ occurs in 60 to 80% of ALCL and carries a favorable prognosis.

ALK– ALCL encompasses a genetic heterogeneity with clinical correlations and carries an overall survival rate of 50%.^{71–74} Those with rearrangement in the DUSP22 gene account for 30% of ALK– ALCL and have a fairly good 5-year survival outcome at 80 to 90%, similar to that of ALK+ ALCL. However, 8% of ALK– ALCL cases with tumor protein 63 (TP63) rearrangements have a very poor outcome. Recurrent mutations of JAK1 and STAT3 and rearrangement in reactive oxygen species 1 and tyrosine kinase 2 (TYK2) genes have been identified in 20% of ALK– ALCL, which result in the activation of STAT3 signaling pathway.

Primary cutaneous ALCL is a rare kind of the CD30+ T-cell proliferative disease. As BIA-ALCL and other ALCL, tumor cells of primary cutaneous ALCL are large anaplastic cells with CD30+ expression and have an activated cytotoxic CD4+ T-cell phenotype. Rearrangement in the DUSP22–interferon regulatory factor 4 and TYK2 are seen in 25 and 10%, respectively, whereas TP63 rearrangements are almost absent.⁶⁹

Treatment

Surgical Management

In contrast to ALK- ALCL, which is typically seen in advanced stages and has poor outcomes, BIA-ALCL has an indolent course and favorable outcomes in most patients. Unlike the normal paradigm for lymphoma management, which involves systemic treatment of chemotherapy and radiotherapy, surgical resection is essential for treatment of BIA-ALCL for it behaving more like a solid tumor than lymphoma.

When BIA-ALCL is confined to the capsule, the disease is almost always localized and surgical treatment alone is usually recommended with implant removal and capsulectomy. In a comparison of the oncologic outcomes in 87 BIA-ALCL patients treated under different therapeutic approaches, the complete surgical excision demonstrated a significantly better long-term disease-free survival compared with other therapeutic modalities ($p < 0.001$).⁶³ As a result, the current NCCN guideline strongly suggests an en bloc surgical resection of the surrounding capsule and removal of the implant. The typical margins used in traditional breast cancer surgery are not required, and lymph node biopsy is required only in the cases with enlarged or suspicious lymph nodes. For early-stage patients, immediate reconstruction may be performed with the insertion of a new round, smooth surface implant or by autologous methods.

After complete resection, surveillance examinations should be continued every 3 to 6 months, and interval imaging of chest, abdomen, and pelvis CT or PET/CT is recommended every 6 months for the first 2 years.

Systemic Treatment

Some rare cases have tumoral dissemination beyond the peri-implant fluid and capsule. For patients in advanced stages, including a tumor mass, lymph node involvement, or distant disease, the disease course behaves similar to the systemic ALK- ALCL and they should be referred for chemotherapy or radiotherapy.^{75,76} The current NCCN guideline recommends the use of brentuximab vedotin, a selective monoclonal antibody of CD30, or a combination regimen, CHOP (Cyclophosphamide, Adriamycin, Vincristine, and Prednisone), which is advocated for residual or disseminated diseases.⁶⁶ Radiation therapy with 24 to 36 Gy should be considered for patients with local residual diseases, positive margins, or surgically unresectable disease with extension in the chest wall.

Prognosis

BIA-ALCL usually has an indolent course except for some rare advanced cases. Several findings, including tumor nodules, bilateral involvement, axillary lymph node dissemination, and histologically infiltrative pattern of the capsule, are known to be associated with aggressive course.⁷⁷

In a retrospective review of 44 patients, those in stage I showed a 100% 3-year overall survival and a 63% 3-year event-free survival.⁶² In another cohort study of 87 patients, stage I patients were found to have a 93% overall survival and 63%

event-free survival at 3 years.⁵⁷ This implies that stage I patients with localized diseases may be at low risk of local recurrence but still have an excellent overall survival. Patients in stages II and III were at higher risk of local recurrence with the 3-year event-free survival at 37 and 29%, respectively.

In addition, in a retrospective study of 19 patients, the presence of a mass was found to have a strong correlation with diffuse infiltration of tumor cells beyond the capsule, which means more advanced disease. The 2-year overall survival rate was significantly greater in patients with a seroma than in those with a mass (100 and 52.5%, respectively).⁴

Surveillance

Central Registration

All confirmed cases of BIA-ALCL should be reported to the government agencies, which is the Ministry of Food and Drug Safety in Korea. The obligation to report all cases to government authorities and the implementation of national and international registries is to calculate the true incidence of the disease and also to provide appropriate support and surveillance for patients with breast implants.

Management for Patients with Breast Implants

Informed consents including a discussion of the risk of ALCL should be mandatory for all patients who are offered breast prostheses. Also, given the widespread use of textured breast implants in the last decades, patients who already underwent breast procedures also should be informed about the risk of ALCL. All patients with breast implants should undergo annual physical examinations, and suspicious cases should be referred to tertiary institutions for prompt investigation and treatment.

However, the current surveillance policy for patients with textured breast devices is to discuss the risk of ALCL without generating unnecessary fear. For asymptomatic patients who are concerned about the potential risk of BIA-ALCL development, no definite evidence supports prophylactic removal of the implant, as the risk of BIA-ALCL development does not outweigh the risk associated with the required surgical procedures. There is also not enough evidence to recommend complete capsulectomy as to reduce the risk of ALCL in the asymptomatic patients.¹²

Recent Studies

Genetic Mutation

Clonal rearrangements of TCR γ or β genes are present in most cases of BIA-ALCL. In a genetic analysis of 36 patients with BIA-ALCL, the absence of rearrangement in the DUSP22 gene was first reported, which was in contrast to a high proportion in systemic or cutaneous ALK- ALCL. Together with the lack of rearrangement in ALK and TP63, BIA-ALCL cells are referred to as "triple-negative" ALCLs.^{78,79}

Through a whole-exome sequencing of DNA derived from the effusion cytology fluid of two BIA-ALCL patients, acquired activating mutations in JAK1 and STAT3 as well as

germline mutation in JAK3 were identified in both cases.⁴⁶ In a targeted next-generation sequencing of seven patients, the JAK1, STAT3, STAT5, and SOCS1 genes involved in the JAK/STAT pathway were located in up to 20% of cases, and TP53 and DNTM3A mutations were also detected in one case.⁴⁷ Although cell lines extracted from effusions are genetically unstable and disclose complex karyotypes, copy number variation analyses revealed some focal changes, including chromosome 19p copy number gain and chromosome 1p and 10p loss in one case.^{46,80}

The cytokine and transcription factor expression profiling of BIA-ALCL showed a similarity with those of primary cutaneous ALCL, including the transcription factors SOCS3, JunB, SATB1, and a cytokine profile suggestive of a Th1 phenotype, which all notably reflect the activation of the JAK/STAT pathway.⁸¹ Altogether, the genetic sequencing data as well as the uniform expression of phosphorylated STAT3 suggest the constitutive activation of the JAK/STAT pathway plays a pivotal role in the pathogenesis of BIA-ALCL.⁸²

T-Cell Immune Reaction

The pattern of cytokine expression of BIA-ALCL shows a predominance in the Th17/Th1 signature, suggesting this as its original cell.⁷⁹ On the other hand, the presence of IL-13 has advocated a Th2 allergic inflammatory response with infiltration of eosinophils and IgE-coated mast cells in clinical specimens of BIA-ALCL. These varying results may be explainable by the microenvironment-induced T-cell plasticity.⁸³ The constitutive JAK/STAT activation by several genetic mutations is known to be associated with the pathogenesis of BIA-ALCL. The inflammatory microenvironment may stimulate an immune response, followed by polyclonal expansion of Th17/Th1 cell subsets with release of inflammatory cytokines and chemokines and accumulation of seroma. The mutations within the pathway, such as the gain-of-function mutation of JAK-STAT3, may subsequently lead to the proliferation of monoclonal T cells and clinical BIA-ALCL.

Conclusion

BIA-ALCL is a rare but an emerging disease with increasing incidence that requires a multidisciplinary team approach for prompt diagnostic workup and treatment. Although the high-risk textured devices have been recalled by the FDA and removed from the market, more cases are expected to be seen frequently over the next decades. As the incidence of BIA-ALCL is expected to increase, it is important for all surgeons and physicians to be aware of this disease entity and acquire thorough knowledge of current evidence-based guidelines and recommendations. Further studies in understanding the genetic mutations and molecular pathways are essential to reveal the exact mechanism of disease progression and to establish the appropriate treatment protocol.

Author Contributions

Conceptualization: H.C. Data curation: J.U.P. Methodology: all authors. Project administration: all authors. Visu-

alization: J.U.P. Writing—original draft: H.Y. Writing—review and editing: H.Y.

Funding

None.

Conflict of Interest

H.C. is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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