Case Report

Analysis of the Molecular Signature of Breast Implant-Associated Anaplastic Large Cell Lymphoma in an Asian Patient

Il-Kug Kim, MD, PhD; Ki Yong Hong, MD, PhD; Choong-kun Lee, MD, PhD; Bong Gyu Choi, MD, PhD; Hyunjong Shin, MD; Jun Ho Lee, MD; Min Kyoung Kim, MD, PhD; Mi Jin Gu, MD, PhD; Jung Eun Choi, MD, PhD; and Tae Gon Kim, MD, PhD

Abstract

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL)—a new category of anaplastic large cell lymphoma associated with textured breast implants—has a distinct variation in incidence and is especially rare in Asia. We report the first case of BIA-ALCL in Korea and present its histological and genetic characteristics. A 44-year-old female patient presented with a typical clinical course and symptoms, including breast augmentation with textured breast implants, late-onset peri-implant effusion, and CD30+ALK− histology, followed by bilateral implant removal and total capsulectomy. For histological analysis, we performed immunohistochemistry of the bilateral breast capsules. For transcriptome analysis, we identified highly upregulated gene sets employing RNA-sequencing and characterized the lymphoma immune cell components. In the lymphoma-associated capsule, CD30+ cells infiltrated not only the lymphoma lesion but also the peritumoral lesion. The morphologies of the myofibroblasts and vessels in the peritumoral lesion were similar to those in the tumoral lesion. We observed strong activation of the JAK/STAT3 pathway and expression of programmed death ligand-1 in the lymphoma. Unlike the molecular profiles of BIA-ALCL samples from Caucasian patients—all of which contained activated CD4+ T cells—the Asian patient’s profile was characterized by more abundant CD8+ T cells. This study contributes to a better understanding of the pathogenesis and molecular mechanisms of BIA-ALCL in Asian patients that will ultimately facilitate the development of clinical therapies.

Level of Evidence: 5

© 2020 The Aesthetic Society. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Drs Il-Kug Kim, Jun Ho Lee, and Tae Gon Kim are professors, Department of Plastic and Reconstructive Surgery, Yeungnam University College of Medicine, Daegu, Korea. Dr Hong is a professor, Department of Plastic and Reconstructive Surgery, Dongguk University Ilsan Hospital, Goyang, Korea. Dr Lee is a clinical professor, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea. Dr Bong Gyu Choi is a resident, Department of Plastic and Reconstructive Surgery, Yeungnam University College of Medicine, Daegu, Korea. Dr Shin is a plastic surgeon, Ulsan BB Plastic Surgery Clinic, Ulsan, Korea. Dr Min Kyoung Kim is a professor, Division of Hematology-Oncology, Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Korea. Dr Gu is a professor, Department of Pathology, Yeungnam University College of Medicine, Daegu, Korea. Dr Jung Eun Choi is a professor, Department of Surgery, Yeungnam University College of Medicine, Daegu, Korea.

Corresponding Author:
Dr Tae Gon Kim, Department of Plastic and Reconstructive Surgery, Yeungnam University College of Medicine, 170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea.
E-mail: kimtg0919@daum.net; Instagram: @kimtg0919
Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a rare type of T-cell lymphoma within the non-Hodgkin's lymphoma (NHL) family. It occurs in patients with breast implants, especially those with textured outer shells. The World Health Organization classifies BIA-ALCL as an ALK-negative T-cell lymphoma that mostly presents as a confined peri-implant effusion or masses within the fibrous capsule, with rare capsular invasion and metastasis; it has an excellent prognosis, similar to primary cutaneous anaplastic large cell lymphomas.1

As the number of patients diagnosed globally with BIA-ALCL increases, analysis has revealed a distinct variation in incidence depending on geographical location or ethnicity, with a relatively low incidence in Asia.2,3 However, cases of BIA-ALCL have recently begun to occur in Asia, including Singapore, Thailand, Japan, and Korea. Here, we report the histological and genetic characteristics of the first case of BIA-ALCL in Korea.

Case Report
Diagnosis and Treatment
In July 2019, a 44-year-old female patient presented with swelling in her right breast 7 years after bilateral breast augmentation with silicone implants (Supplemental Figure 1). A breast ultrasound showed fluid collection surrounding the right breast implant. The patient underwent right breast implant removal and capsule biopsy. Simultaneously, >500 mL of peri-implant effusion was removed. The implant was a BIOCELL silicone-filled textured breast implant (Allergan Inc., Irvine, CA). Atypical cell infiltration of the breast capsule was observed by hematoxylin and eosin (H&E) staining. The patient was transferred to our hospital for further evaluation.

Immunohistochemical analysis of the capsule tissue revealed the expression of CD3 and CD30 in the absence of ALK and CD20 expression, resulting in a diagnosis of BIA-ALCL (Supplemental Figure 2). Fluorodeoxyglucose uptake in the bilateral axillae was observed via positron emission tomography-computed tomography (Figure 1A,B). Subsequently, removal of the contralateral left breast implant, total bilateral capsulectomy of the breasts, and biopsies of the bilateral axillary lymph nodes were performed. Grossly, we observed multiple hard, immobile masses of various sizes below the inner surface of the right breast capsule (Figure 1C,D). Histological analysis by H&E staining revealed that the thickened peri-implant capsule had been infiltrated by multiple lymphomas (Figure 1E,F). Fluorodeoxyglucose uptake in the right axilla was identified as an extension of the right breast lymphoma, and uptake in the left axilla was the result of reactive hyperplasia. The left breast capsule was normal, and we did not observe involvement of the lymphoma in the bilateral axillary nodes or distant metastases. We performed chemotherapy and radiation therapy according to the National Comprehensive Cancer Network guidelines for stage IIA (T4NOM0) lymphoma.4 Eight months postoperatively, the patient presented no evidence of recurrence (Supplemental Figure 3).

Immunohistochemical Analysis
In H&E-stained sections, we identified 2 distinct lesions—tumoral and peritumoral—in the lymphoma-associated capsule. The distribution of BIA-ALCL cells was examined by immunostaining for CD30. There were no CD30+ cells in the contralateral capsule (Figure 2A). As expected, the tumoral lesion had been fully infiltrated by CD30+ cells in the BIA-ALCL capsule (Figure 2A). In addition, many CD30+ cells were dispersed in the peritumoral lesion (Figure 2A). These findings indicated that dispersed CD30+ cells in the peritumoral lesion of a BIA-ALCL capsule support total capsulectomy even in cases that present with a distinct mass in the capsule.

Next, we evaluated the distribution of α-smooth muscle actin (αSMA)+ myofibroblasts that play a pivotal role not only in fibrosis but also in tumor progression, invasion, and metastasis. Because BIA-ALCL tumor masses are located in the peri-implant capsule, we hypothesized a close relationship between tumor cells and myofibroblasts and consequently examined the distribution and morphology of myofibroblasts in this patient. We detected αSMA+ myofibroblasts in both lymphoma-associated and contralateral capsules (Figure 2B). However, αSMA+ myofibroblasts in the BIA-ALCL capsule were more abundant with more filopodia than those in the contralateral capsule (Figure 2B). The distribution and morphology of αSMA+ myofibroblasts in the peritumoral lesion were similar to those in the tumoral lesion (Figure 2B). We further examined the vascularity of the bilateral capsules by immunofluorescent staining for CD31. The vessels in the BIA-ALCL capsule had a larger diameter and appeared at a higher density than those in the contralateral capsule (Figure 2C). Interestingly, the morphological features of the vessels in the peritumoral lesion were similar to those of the vessels in the tumoral lesion. These data suggest that the histological characteristics of the peritumoral lesion in the capsule are very similar to those of the lymphoma itself.

Molecular Analysis
To gain comprehensive molecular insights into the first Korean case of BIA-ALCL, we performed a transcriptomic analysis comparing the tumoral lesion with the contralateral capsule as a control. Many of the most highly upregulated hallmark gene sets were related to inflammatory response (Figure 3A). Gene set enrichment analysis identified activation of the Janus kinase/signal transducer and activator of transcription.
Figure 1. Preoperative positron emission tomography-computed tomography (PET-CT) images showed fluorodeoxyglucose (FDG) uptake (arrow) in the right axilla (A) and right peri-implant capsule tissue (B). FDG uptake in the right axilla was postoperatively demonstrated to be an extension of the breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) rather than lymph node metastasis. Gross images of the outer (C) and inner (D) surfaces of the right peri-implant capsule infiltrated with BIA-ALCL. Multiple hard, immobile masses of various sizes were observed below the inner surface of the capsule. Representative images of the peri-implant capsule from the contralateral normal breast (E) and the breast affected by BIA-ALCL (F) stained with hematoxylin and eosin (H&E). The lymphoma capsule was divided into 2 parts: the tumoral and peritumoral lesions. Scale bars = 3 mm.
Figure 2. The distribution of CD30+ lymphoma cells, αSMA+ myofibroblasts, and blood vessels of peri-implant capsules. (A) We observed no CD30+ cells in the contralateral capsule (left), dispersed CD30+ cells (arrows) in the peritumoral lesion (center), and clustered CD30+ cells in the tumoral lesion (right). (B) Few αSMA+ myofibroblasts were observed in the contralateral capsule (left). Many αSMA+ myofibroblasts with an aggressive morphology featuring many filopodia were observed in the peritumoral (center) and tumoral (right) lesions. (C) The vascularity of peri-implant capsules as assessed by CD31 immunofluorescent staining in the contralateral capsule (left), peritumoral lesion (center), and tumoral lesion (right). Scale bars = 100 μm.
Figure 3. (A) The top 10 most differentially expressed hallmark gene sets in breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) compared to the control. Gene set enrichment analysis (GSEA) (B) and heatmap (C) of the top 15 most upregulated genes involved in IL6/Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) signaling. (D) Estimated absolute fraction score of the major immune cell subsets in the lymphoma (T) and contralateral (C) capsules. (E) The heatmap figure was generated with the CIBERSORT webserver using the built-in LM22 immune cell gene signature. The inferred composition of the 22 immune cell subsets in BIA-ALCL (T) and contralateral capsule (C) is shown. NES, normalized enrichment score.
3 (JAK/STAT3) pathway in the tumor (Figure 3B,C) in accord-
ance with recently reported activating mutations in related
genes in BIA-ALCL.5-7 The other upregulated gene sets in-
cluded allograft rejection, TGF-beta signaling, and interferon
gamma response (Supplemental Figure 4).

Next, we performed a CIBERSORT analysis to esti-
mate the abundance of immune-cell subtypes in the
lymphoma.8 The BIA-ALCL capsule contained more
CD8+ T cells and regulatory T cells than the contralat-
eral capsule (Figure 3D,E). We confirmed the abundance
of CD8+ T cells in the tumoral lesion of our patient by
immunohistochemistry (Figure 4A).

IFN-γ, which was upregulated in our transcriptomic anal-
ysis (Figure 3A), upregulates programmed death ligand-1
(PD-L1) expression in solid tumor cells through JAK-STAT
signaling.9 Thus, we evaluated PD-1/PD-L1 signaling in the
tumor. Immunohistochemical staining revealed strong ex-
pression of PD-L1 in the tumor cells of BIA-ALCL, with a
combined positive score of 100 and a tumor proportion
score ≥99% (Figure 4B).

**DISCUSSION**

In Korea, silicone breast implants with textured surfaces
were approved in 2007, and 213,000 units manufactured
by 6 different companies have been implanted in Korean
patients since then.10 Among these, 114,000 breast im-
plants (54%) were manufactured by Allergan. The cos-
metic industry in Asia, including Korea, has undergone
recent growth along with an expansion in breast implant
surgery.3 Although the incidence of BIA-ALCL in Asia has
been low, recent reports of BIA-ALCL are emerging in
Asia, including Japan11 and Thailand12 (Table 1). In August
2019, the first Korean BIA-ALCL case was officially an-
nounced by the Ministry of Food and Drug Safety and the
Korean Society of Plastic and Reconstructive Surgeons.
We analyzed the histological and genetic characteris-
tics of the capsule specimens from this patient to com-
pare features with those of previously reported cases in
Caucasian patients.

For histological analysis, we divided the BIA-ALCL
capsule into the tumoral and peritumoral lesions and
compared them with the contralateral capsule. The abun-
dance of CD30+ cells and the morphology of αSMA+
myofibroblasts and CD31+ vessels in the peritumoral lesion
were significant, suggesting that the peritumoral lesion
should be considered a potential site of tumor progres-
sion. In accordance with this conclusion and the National
Comprehensive Cancer Network guidelines, we recom-
mand total capsulectomy for cases of BIA-ALCL.
BIA-ALCL shares molecular and genomic similarities with systemic anaplastic large cell lymphoma in the absence of the typical gene rearrangements involving ALK, DUSP22, and TP63. In addition, the JAK/STAT3 pathway is constitutively activated in BIA-ALCL, partly attributed to point mutations in JAK1 and STAT3. Consistent with the previously suggested etiopathogenesis of BIA-ALCL, our transcriptomic analysis showed overexpression of genes related to immune-mediated chronic inflammation and the JAK/STAT3 pathway.

Because BIA-ALCL is rarely reported in Asia, anaplastic large cell lymphoma itself is also relatively infrequent in Asia compared with Europe. Prevalence of JAK/STAT mutation among Asian BIA-ALCL cases or anaplastic large cell lymphoma of any type was also not reported. However, several studies have shown an association between Asian T-cell lymphoma and evidence of Epstein-Barr virus infections. In addition, several genetic polymorphisms associated with the risk of NHL suggest that single nucleotide polymorphisms in TNF and IL-10 are associated with the risk of NHL. The mechanisms by which genetic predisposition or gene–environment interactions may enhance or reduce the risk of developing lymphoma remain largely unexplored areas of research to date; however, these factors may affect geographical differences in the prevalence of BIA-ALCL.

Our transcriptomic analysis comparing the tumoral lesion and contralateral capsule from our patient revealed a unique transcriptional signature for Korean BIA-ALCL. PD-L1 is transcriptionally regulated by STAT3. Our CIBERSORT and immunohistochemistry analyses revealed overexpression of PD-L1 in the tumor and marked infiltration by CD8+ T cells. A previous CIBERSORT analysis of BIA-ALCL in Caucasian patients showed a molecular profile consistent with the presence of activated CD4+ memory T cells and regulatory T cells. Recently, the expression of PD-L1 in the BIA-ALCL capsule was reported, suggesting that the PD-L1 pathway may constitute a promising therapeutic target for BIA-ALCL.

To the best of our knowledge, our comprehensive molecular analysis is the first to suggest the possibility that the PD-L1 signaling pathway drives BIA-ALCL carcinogenesis via activation of the JAK/STAT3 pathway.

Tumor cells constitutively express PD-L1 for various reasons, including genetic amplification of chromosome 9 containing the PD-L1, PD-L2, and interferon receptor adapter JAK2 loci. PD-L1 expression in tumor cells can also be induced by type I and II interferons produced by infiltrating T cells. In the present case, both constitutive and inducible expression of PD-L1 are possible mechanisms. Our results collectively suggest immune evasion as a carcinogenesis mechanism in this case of BIA-ALCL. However, the strength and applicability of our findings are limited by the analysis of samples from only a single patient. Further in-depth molecular analyses of Korean and/or Asian BIA-ALCL samples are warranted to determine whether the immune evasion-related mechanism of carcinogenesis is relevant only in the present case or more broadly in Asian BIA-ALCL. If the mechanism is found to be commonly implicated in the disease, it may be possible to adapt anti-PD-1/PD-L1 immune checkpoint blockade as a therapeutic strategy for sensitive cases of BIA-ALCL.

**CONCLUSIONS**

Herein we present the first case of BIA-ALCL in Korea. The patient presented with a history of breast augmentation with textured breast implants, late-onset peri-implant effusion, and CD30+ALK− histology. In the capsule affected by BIA-ALCL, the lymphoma and the peritumoral lesion shared abundant CD30+ cell infiltration as well as similar myofibroblasts and vessel morphology. Employing RNA-sequencing, we identified activation of the JAK/STAT3 pathway and strong PD-L1 expression in lymphoma. However, unlike the Caucasian BIA-ALCL molecular profile—characterized by activated CD4+ memory T cells—the molecular profile of the lymphoma in our patient was characterized by a CD8+ T-cell phenotype. Although our study covers only 1 case, we anticipate that it will contribute to a better understanding of the pathogenesis and molecular mechanisms involved in BIA-ALCL, thereby providing insight into potential therapeutic strategies.
Supplemental Material
This article contains supplemental material located online at www.aestheticsurgeryjournal.com.

Acknowledgments
Drs Il-Kug Kim, Ki Yong Hong, and Choong-kun Lee equally contributed to this work as co-first authors.

Disclosures
The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

Funding
This research was supported by the National Research Foundation of Korea (NRF-2018R1C1B6004618, 2019M3E5D1A02068102, and 2015R1A5A2090124 to Il-Kug Kim; NRF-2020R1C1004461 to Choong-kun Lee; and NRF-2019R1F1A1063050 to Ki Yong Hong).

REFERENCES
1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-2390.
2. Brody GS, Deapen D, Taylor CR, et al. Anaplastic large cell lymphoma occurring in women with breast implants: analysis of 173 cases. Plast Reconstr Surg. 2015;135(3):695-705.
3. Collett DJ, Rakhorst H, Lennox P, Magnusson M, Cooter R, Deva AK. Current risk estimate of breast implant-associated anaplastic large cell lymphoma in textured breast implants. Plast Reconstr Surg. 2019;143(3S A Review of Breast Implant-Associated Anaplastic Large Cell Lymphoma):305-405.
4. Ciemens MW, Jacobsen ED, Horwitz SM. 2019 NCCN consensus guidelines on the diagnosis and treatment of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL). Aesthet Surg J. 2019;39(Suppl_1):S3-S13.
5. Blombery P, Thompson ER, Jones K, et al. Whole exome sequencing reveals activating JAK1 and STAT3 mutations in breast implant-associated anaplastic large cell lymphoma anaplastic large cell lymphoma. Haematologica. 2016;101(9):e387-e390.
6. Letourneau A, Maerevoet M, Milowich D, et al. Dual JAK1 and STAT3 mutations in a breast implant-associated anaplastic large cell lymphoma. Virchows Arch. 2018;473(4):505-511.
7. Di Napoli A, Jain P, Duranti E, et al. Targeted next generation sequencing of breast implant-associated anaplastic large cell lymphoma reveals mutations in JAK/STAT signalling pathway genes, TP53 and DNMT3A. Br J Haematol. 2018;180(5):741-744.
8. Newman AM, Liu CL, Green MR, et al. Robust enumeration of cell subsets from tissue expression profiles. Nat Methods. 2015;12(5):453-457.
9. Mimura K, Teh JL, Okayama H, et al. PD-L1 expression is mainly regulated by interferon gamma associated with JAK-STAT pathway in gastric cancer. Cancer Sci. 2018;109(1):43-53.
10. Oh JS, Jeong JH, Myung Y, et al. BellaGel breast implant: 6-year results of a prospective cohort study. Arch Plast Surg. 2020;47(3):235-241.
11. Ohishi Y, Mitsuda A, Ejima K, et al. Breast implant-associated anaplastic large-cell lymphoma: first case detected in a Japanese breast cancer patient. Breast Cancer. 2020;27(3):499-504.
12. Thienpaitoon P, Disphanurat W, Wannissorn N. Breast implant-associated anaplastic large cell lymphoma in an Asian patient: the first case report from Thailand. Arch Plast Surg. 2020;47(5):478-482.
13. Oishi N, Miranda RN, Feldman AL. Genetics of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL). Aesthet Surg J. 2019;39(Suppl_1):S14-S20.
14. Blombery P, Thompson ER, Prince HM. Molecular drivers of breast implant-associated anaplastic large cell lymphoma. Plast Reconstr Surg. 2019;143(3S A Review of Breast Implant-Associated Anaplastic Large Cell Lymphoma):595-64S.
15. Rastogi P, Riordan E, Moon D, Deva AK. Theories of etiopathogenesis of breast implant-associated anaplastic large cell lymphoma. Plast Reconstr Surg. 2019;143(3S A Review of Breast Implant-Associated Anaplastic Large Cell Lymphoma):23S-29S.
16. Lechner MG, Megiel C, Church CH, et al. Survival signals and targets for therapy in breast implant-associated ALK–anaplastic large cell lymphoma. Clin Cancer Res. 2012;18(17):4549-4559.
17. Kadin ME, Deva A, Xu H, et al. Biomarkers provide clues to early events in the pathogenesis of breast implant-associated anaplastic large cell lymphoma. Aesthet Surg J. 2016;36(7):773-781.
18. Kadin ME, Morgan J, Kouttab N, et al. Comparative analysis of cytokines of tumor cell lines, malignant and benign effusions around breast implants. Aesthet Surg J. 2020;40(6):630-637.
19. Vose J, Armitage J, Weisenburger D; International T-Cell Lymphoma Project. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol. 2008;26(25):4124-4130.
20. Cho EY, Kim KH, Kim WS, Yoo KH, Koo HH, Ko YH. The spectrum of Epstein-Barr virus-associated lymphoproliferative disease in Korea: incidence of disease entities by age groups. J Korean Med Sci. 2008;23(2):185-192.
21. Alexander DD, Mink PJ, Adami HO, et al. The non-Hodgkin lymphomas: a review of the epidemiologic literature. Int J Cancer. 2007;120(Suppl 12):1-39.
22. Di Napoli A, De Cecco L, Piccaluga PP, et al. Transcriptional analysis distinguishes breast implant-associated anaplastic large cell lymphoma from other peripheral T-cell lymphomas. Mod Pathol. 2019;32(2):216-230.
23. Bianchi A, Ferrari S, Gullotta G, Grasso A, Annibali O. PD-1/ PD-L1 checkpoint in breast implant-associated anaplastic
large cell lymphoma: a case report. *Biomed J Sci and Tech Res*. 2018;3(2):3105–3108.

24. Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. *Blood*. 2010;116(17):3268-3277.

25. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin’s lymphoma. *N Engl J Med*. 2015;372(4):311-319.

26. Rooney MS, Shukla SA, Wu CJ, Getz G, Hacohen N. Molecular and genetic properties of tumors associated with local immune cytolytic activity. *Cell*. 2015;160(1-2):48-61.

27. Taube JM, Klein A, Brahmer JR, et al. Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. *Clin Cancer Res*. 2014;20(19):5064-5074.

28. Tumeh PC, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature*. 2014;515(7528):568-571.