KOREA

Breast Surgery

Case Report

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

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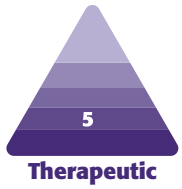
Abstract

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



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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 lymph nodes or distant metastases. We performed chemotherapy and radiation therapy according to the National Comprehensive Cancer Network guidelines for stage IIA (T4N0M0) 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 ($\alpha SMA)^+$ 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

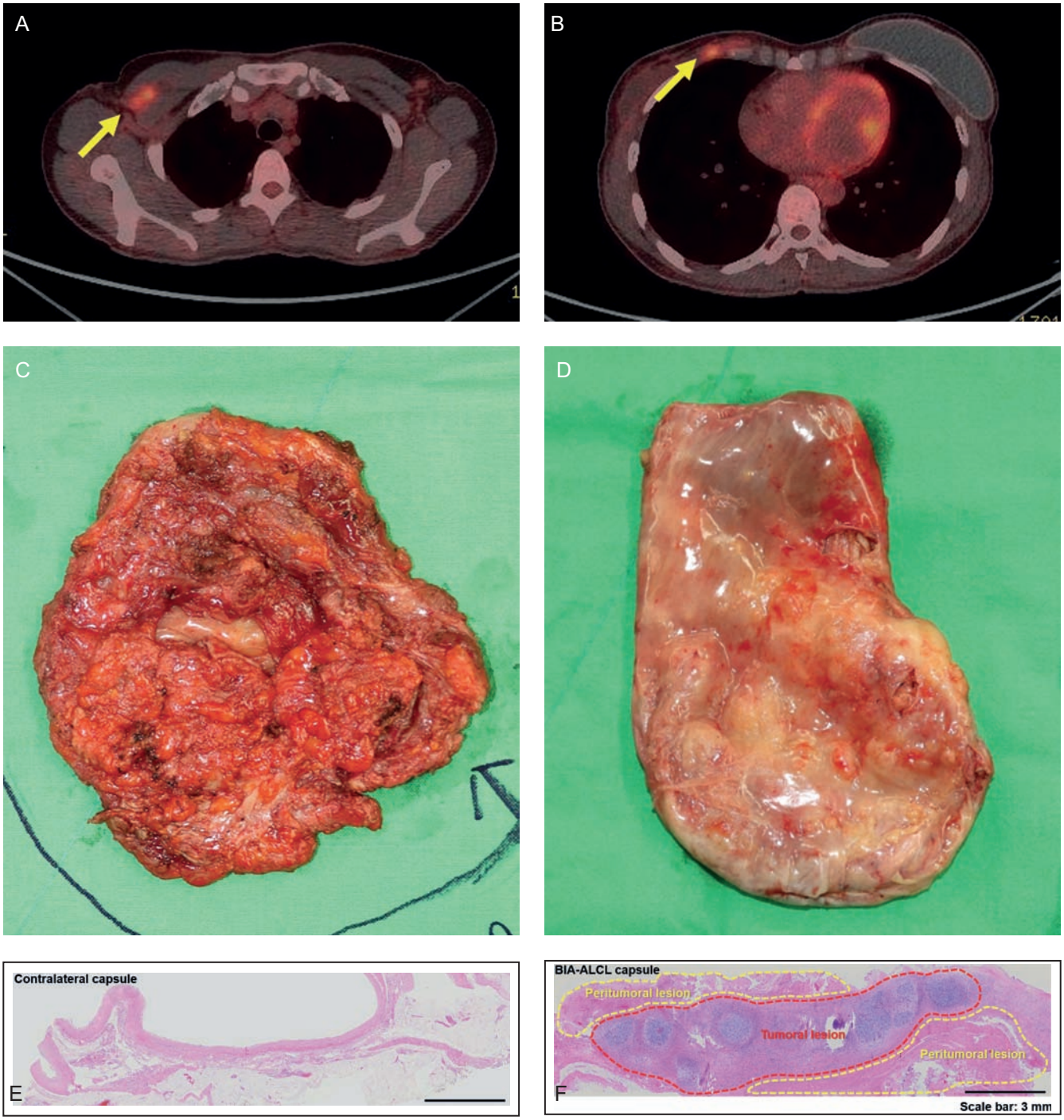

Figure 1. Preoperative positron emission tomography-computed tomography (PET-CT) images showed fluorodeoxyglucose (FDG) uptake (arrow) in the right axilla (A) and right peri-implant capsule tissue (B). FDG uptake in the right axilla was postoperatively demonstrated to be an extension of the breast implant-associated 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.

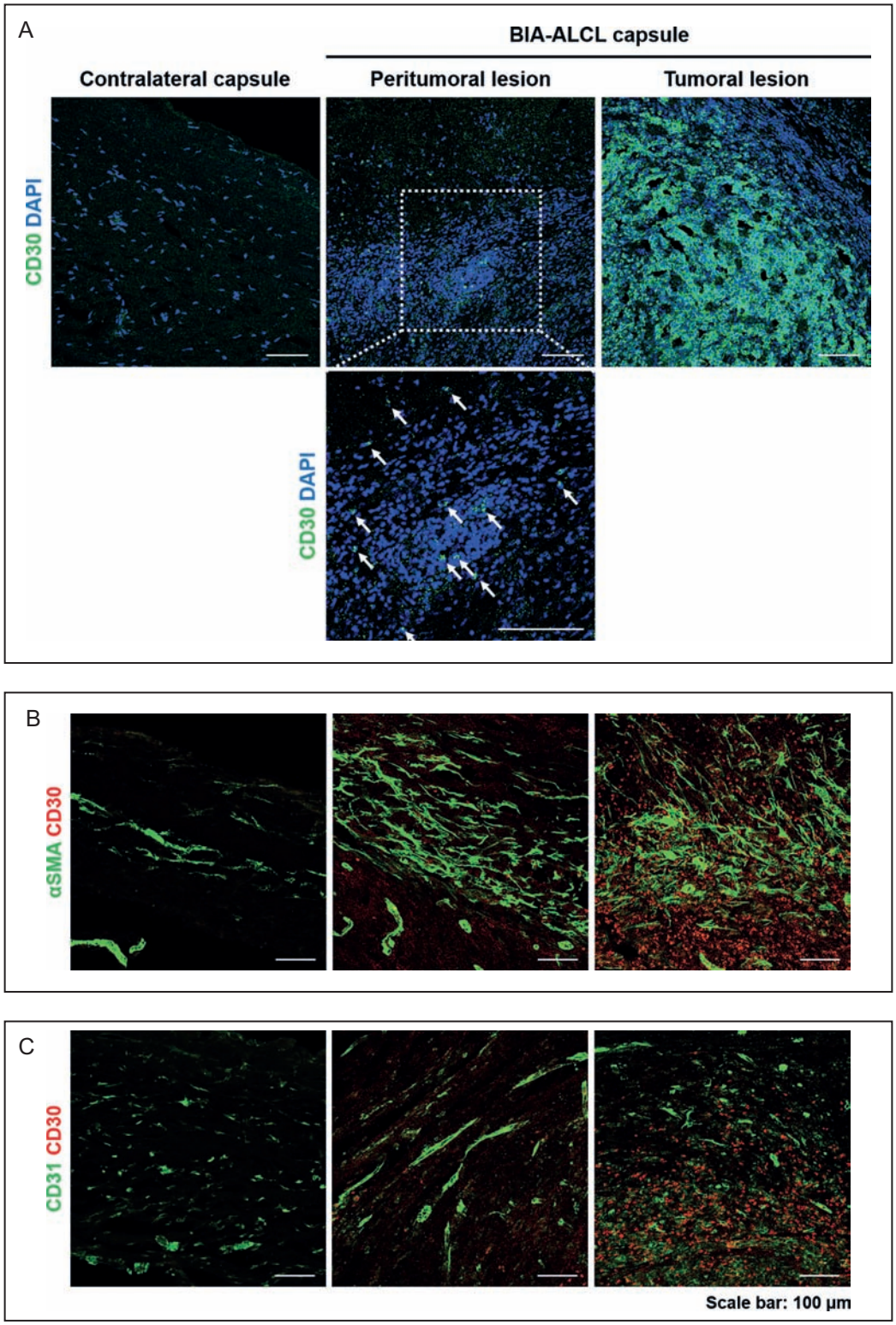

Figure 2. The distribution of CD30$^+$ lymphoma cells, αSMA$^+$ myofibroblasts, and blood vessels of peri-implant capsules. (A) We observed no CD30$^+$ cells in the contralateral capsule (left), dispersed CD30$^+$ cells (arrows) in the peritumoral lesion (center), and clustered CD30$^+$ cells in the 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.

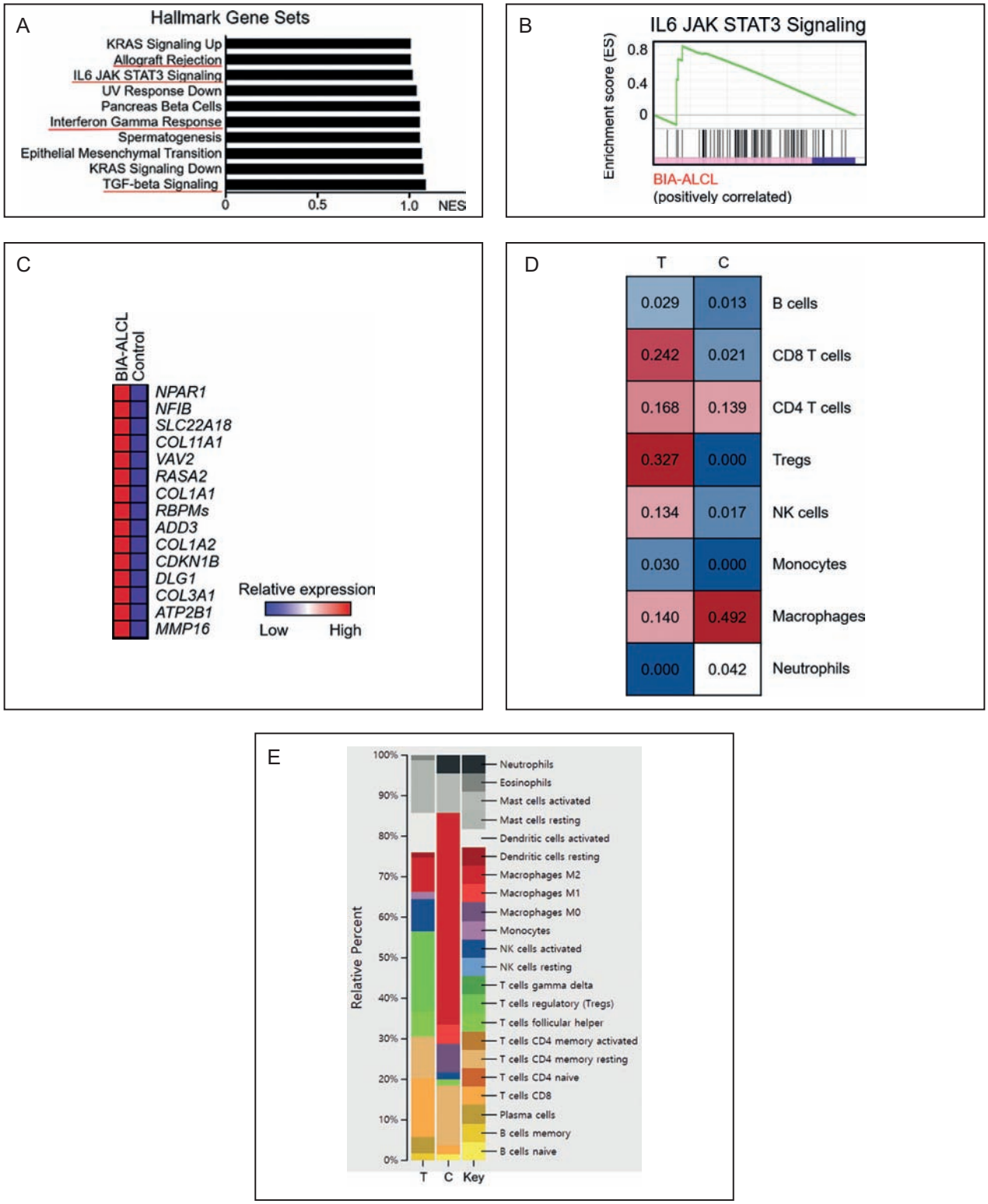

Figure 3. (A) The top 10 most differentially expressed hallmark gene sets in breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) compared to the control. Gene set enrichment analysis (GSEA) (B) and heatmap (C) of the top 15 most upregulated genes involved in IL6/Janus kinase/signal transducer 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.

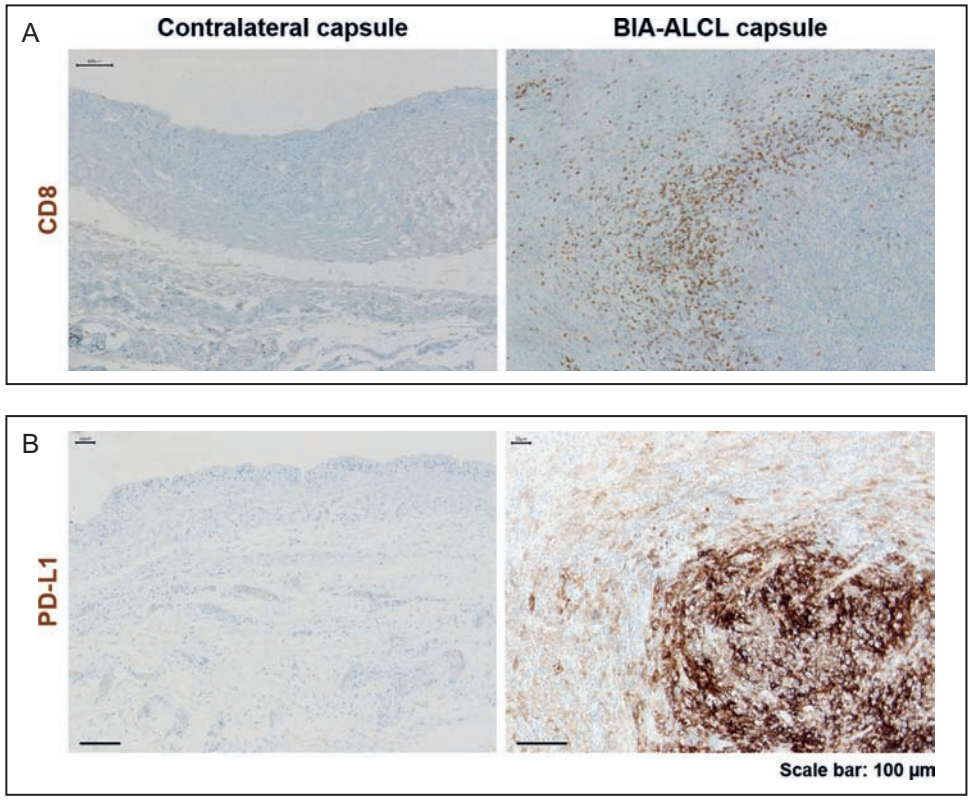

Figure 4. Representative immunohistochemistry images of CD8 (A) and PD-L1 (B) expression in the contralateral capsule and the breast implant-associated anaplastic large cell lymphoma capsule. Scale bars = 100 μm.

3 (JAK/STAT3) pathway in the tumor (Figure 3B,C) in accordance with recently reported activating mutations in related genes in BIA-ALCL.[5-7] The other upregulated gene sets included allograft rejection, TGF-beta signaling, and interferon gamma response (Supplemental Figure 4).

Next, we performed a CIBERSORT analysis to estimate 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 contralateral 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 analysis (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 expression 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 implants (54%) were manufactured by Allergan. The cosmetic 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 Japan[11] and Thailand[12] (Table 1). In August 2019, the first Korean BIA-ALCL case was officially announced by the Ministry of Food and Drug Safety and the Korean Society of Plastic and Reconstructive Surgeons. We analyzed the histological and genetic characteristics of the capsule specimens from this patient to compare 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 abundance 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 progression. In accordance with this conclusion and the National Comprehensive Cancer Network guidelines, we recommend total capsulectomy for cases of BIA-ALCL.

Table 1. Clinical and demographic characteristics of BIA-ALCL in Asia

Country	Implant indication	Laterality	Age diagnosing BIA-ALCL (y)	Implant duration (y)	Clinical presentation	Manufacturer	Texture type	Stage	Treatment	Follow-up period
Japan[11]	Reconstruction	Left	67	17	Effusion	Allergan	Biocell	IV	Surgery, CTx	7 mo
Thailand[12]	Cosmetic	Left	32	3	Effusion	Silimed	Polyurethane	IA	No	2 y
Korea	Cosmetic	Right	44	7	Effusion	Allergan	Biocell	IIA	Surgery, CTx, RT	8 mo

BIA-ALCL, breast implant-associated anaplastic large cell lymphoma; CTx, chemotherapy; RT, radiation therapy.

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*.[13,14] In addition, the JAK/STAT3 pathway is constitutively activated in BIA-ALCL, partly attributed to point mutations in JAK1 and STAT3.[5-7] Consistent with the previously suggested etiopathogenesis of BIA-ALCL,[15-18] 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.[19] 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.[20] 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[21]; 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.[22] 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.[13,23] 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.[24-26] PD-L1 expression in tumor cells can also be induced by type I and II interferons produced by infiltrating T cells.[27,28] 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.

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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.

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