Breast Implant–Associated CD30 Negative Peripheral T-Cell Lymphoma, NOS

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Breast implant–associated peripheral T-cell lymphoma (BIA-PTCL) was first reported in 1997. Since then, 2 clinical variants emerged, PTCL presenting as a periprosthetic seroma or a more aggressive infiltrative mass. After 2 decades, this PTCL received provisional classification as breast implant–associated anaplastic lymphoma kinase (ALK)–negative anaplastic large cell lymphoma (BIA-ALCL). Diagnosis is based on cytology, evidence of T-cell clonality, immunohistochemistry (IHC) for CD30 and T-cell markers, and ALK negativity. While T-cell phenotype varies, cases have been consistently CD30 positive. Consequently, CD30 has been advocated as a screening test to differentiate benign seromas. Here, we report a case of BIA-PTCL, not otherwise specified (NOS) presenting as a periprosthetic mass with no CD30 expression that was fatal. While resembling the infiltrative variant of BIA-ALCL, cell surface markers were most similar to that of monomorphic epithelioid T-cell lymphoma (MEITL). While this case is atypical, it suggests that even with CD30 negativity, clinicians should maintain a high index of suspicion in patients with concerning clinical or pathologic features, and BIA-PTCL, NOS with a silent phenotype should be considered. Further research into implant-associated PTCL is needed.

A 67-year-old Hispanic-American female presented to the emergency room after being found wandering in the street, disoriented. She described gradual loss of vision and could only appreciate light perception and finger movements. When her vision worsened, she saw an optometrist and started prednisone, now at 20 mg oral daily, without relief. History was remarkable for bilateral breast implant placement 42 years prior for augmentation. She denied smoking or alcohol and was a retired clerical worker. Review of systems noted significant weight loss and left breast swelling. On examination, there was a large breast mass lateral to the prosthesis with induration extending medially and left breast swelling. After 2 decades, this PTCL received provisional classification as BIA-ALCL was first reported in 1997. Since then, 2 clinical variants emerged, PTCL presenting as a periprosthetic seroma or a more aggressive infiltrative mass. 2-4 The exact incidence of BIA-ALCL is unknown but it is estimated that the lifetime prevalence is 1 per 30,000 patients with textured breast implants, although a prospective study suggested that the incidence may be closer to 1 case per 4000. Most cases present after 7-10 years.
years and at a median age of 50-60 years,\(^3,9\) although there are reports >30 years from surgery, as in the present case.\(^10\)

Our current understanding is that there are 2 clinical variants of BIA-ALCL, presenting as either the more common periprosthetic seroma or an infiltrative mass.\(^2,4\) These 2 variants have different prognoses, with the infiltrative variant having more aggressive biology and worse outcomes. However, no specific pathologic features differentiating these 2 groups have been elucidated.\(^3,11\) Indeed, it is unclear if these are distinct subtypes, or simply represent a spectrum of disease.

BIA-ALCL is thought to develop after years of implant-induced inflammation inducing dysplastic changes from chronic antigen stimulation. To date, the 2 most frequently discussed etiological candidates are inflammation from textured implants and chronic bacterial stimulation.\(^12\) Added to this is a recent hypothesis on prosthesis-associated tissue hypoxia.\(^11\) Aberrant gene expression is of course most likely involved in the oncogenic progression from a chronic inflammatory state to a full-blown malignancy. Recurrent JAK1 and STAT3 gene mutations have been identified and, like many other ALCLs, also identified have been mutations in DNMT3A, TP53, and SOCS.\(^13,15\) However, even in the analyses of these small series, there have been cases evaluated with no somatic mutations. Recently, RNA sequencing and gene set enrichment analysis comparing eleven BIA-ALCLs to 24 non–BIA-ALCLs identified upregulation of hypoxia signaling genes including

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**Figure.** PET-CT imaging demonstrating intensely avid periprosthetic lymphoma mass in the transverse (A), coronal (B) and sagittal (C) planes. PET-CT = positron emission tomography-computed tomograph.

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**Table**

| Pathological Features | Phenotypical Features | EBV Status | Cytogenetic and Molecular Features |
|-----------------------|----------------------|------------|----------------------------------|
| Diffuse lymphoid infiltrate composed of large atypical cells with irregular nuclear contours, fine chromatin, conspicuous mitotic activity, and abundant eosinophilic cytoplasm | Surface markers: CD2, CD3, CD56, Granzyme B, Perforin, c-MYC, BCL-2, MUM1, and CD20 (weak); Ki67 proliferative index >90% | Positive: EBER, T-cell receptor Gamma gene rearrangement, BCL2 deletion or chromosome 18 monosomy | Negative: BCL6 rearrangement, MYC rearrangement/amplification, IgH/BCL2 translocation |

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*EBV* = Epstein-Barr virus.
VEGFA, VEGFB, SLC2A3 (encoding GLUT3), and carbonic anhydrase-9. 

Currently, diagnosis of BIA-ALCL is based on cytology, evidence of T-cell clonality, and IHC. Morphologically, the tumor is comprised of large, pleomorphic cells with abundant cytoplasm, and horseshoe-shaped or “embryoid” nuclei with prominent nucleoli. With the exception of prominent nucleoli, the case presented had this morphology, and as noted, also T-cell clonality. On IHC, BIA-ALCL typically demonstrates strong and uniform membranous expression of CD30 and lacks ALK expression. Other T-cell antigens have been reported expressed variably, with the most common being CD4 (79%-84%), CD43 (80%-95%), CD3 (28%-46%), CD45 (36%), and CD2 (30%-41%). 5,10,16 Expression of CD5, CD7, CD8, CD15, or CD56 is less common. MUM1, Granzyme B, TIA-1, and BCL2 have a high prevalence. 10,16 Our case expressed CD2, CD3, CD56, Granzyme B, Perforin, C-MYC, BCL-2, MUM1, and CD20 (weak). Weak expression of CD20 has been reported in PTCL, NOS.

While T-cell phenotype has been variably reported, cases to date have been consistently CD30 positive. For instance, in a 2019 expanded safety analysis, 246 cases reported positive. 3 Nevertheless, IHC has not been reported in all cases, and for example, in this series, 57% of cases did not have CD30 results available. 3 National Comprehensive Cancer Network guidelines now recommend that scant or rare CD30-positive lymphocytes with normal morphology can be considered a normal finding with no further investigation. 17 One group has recently examined a CD30 enzyme-linked immunosorbent assay with the aim of a lower-cost screening test more widely available than flow cytometry and IHC, and use to screen suspicious peri-implant fluid collections. 18 Other groups are investigating unique cytokine profiles including IL-13, and molecular signatures to differentiate BIA-ALCL. 11,15,19 Apart from the significance of CD30 in diagnosis, it is also important for management. Brentuximab vedotin has been used in cases of BIA-ALCL.

This case of BIA-PTCL, NOS presented a large periprosthetic mass with the dilemma of no CD30 expression. The disease was extremely aggressive with a high proliferation index and CNS involvement, and ultimately resulted in death. Clinically, the disease course resembled the infiltrative type of BIA-ALCL. Cytology, ALK testing, and T-cell clonality were similar to reported cases of BIA-ALCL. However, the cell surface markers were most similar to that of MEITL. Both MEITL and BIA-ALCL are novel diseases classified in 2016 and driven by T-cell activation. MEITL was previously known as type II enteropathy–associated T-cell lymphoma but it was given a new name due to its distinctive nature and lack of association with celiac disease. It should be noted that MEITL is an intestinal lymphoma and does not occur in the setting of implants. In this case, it could easily be excluded based on the clinical setting, tumor site, as well as histology—MEITL tumor cells are monomorphic and small to medium in size, infiltrating the intestinal epithelium. The adjacent “normal” mucosa demonstrates villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis. There is no inflammatory background in MEITL. Most cases of MEITL are derived from γδ T cells and, similar to BIA-ALCL, the JAK-STAT pathway has been implicated in MEITL. 1,20

While this case is rare, it suggests that even with CD30 negativity, clinicians should maintain a high index of suspicion in patients with concerning clinical or pathologic features, and consider BIA-PTCL, NOS with silent phenotype. As more cases of BIA-ALCL are reported, we anticipate more data on atypical cases. Further research into BIA-PTCL, NOS is needed.

We have presented the first case of BIA-PTCL, NOS occurring as CD30 negative disease with a surface phenotype similar to MEITL. The disease was clinically similar to the infiltrative mass variant of BIA-ALCL, being aggressive and resulting in death. This case suggests that CD30 by itself is not 100% sensitive to exclude BIA-PTCL, NOS. Similar cases need to be reported to help define this disease better and further research into implant-associated PTCL in general is urgently needed.

References
1. Keech JA Jr, Creech BJ. Anaplastic T-cell lymphoma in proximity to a saline-filled breast implant. Plast Reconstr Surg. 1997;100:545–555.
2. FDA. Medical device reports of breast implant-associated anaplastic large cell lymphoma. https://www.fda.gov/medical-devices/breast-implants/medicaldevice-reports-breast-implant-associated-anaplasic-large-cell-lymphoma. Last accessed November 9, 2020.
3. Laurent C, Delas A, Gauld P, et al. Breast implant-associated anaplastic large cell lymphoma: two distinct clinicopathological variants with different outcomes. Ann Oncol. 2016;27:306–314.
4. Miranda RN, Aladily TN, Prince HM, et al. Breast implant-associated anaplastic large-cell lymphoma: long-term follow-up of 60 patients. J Clin Oncol. 2014;32:114–120.
5. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127:2375–2390.
6. Giardini R, Piccoli C, Rilke F. Primary non-Hodgkin’s lymphomas of the female breast. Cancer. 1992;69:725–735.
7. Talwalkar SS, Miranda RN, Valbuena JR, et al. Lymphomas involving the breast: a study of 106 cases comparing localized and disseminated neoplasms. Am J Surg Pathol. 2008;32:1299–1309.
8. McGuire P, Reisman NR, Murphy DK. Risk factor analysis for capsular contracture, malposition, and late seroma in subjects Receiving Natrelle 410 form-stable silicone breast implants. Plast Reconstr Surg. 2017;139:1–9.
9. Loch-Wilkinson A, Beath KJ, Knight RJW, et al. Breast implant-associated anaplastic large cell lymphoma in Australia and New Zealand: high-surface-area textured implants are associated with increased risk. Plast Reconstr Surg. 2017;140:645–654.
10. Barbé E, de Boer M, de Jong D. A practical cytological approach to the diagnosis of breast-implant associated anaplastic large cell lymphoma. Cytopathology. 2019;30:363–369.
11. Oishi N, Hundal T, Phillips T, et al. Molecular profiling reveals a hypoxia signature in breast implant-associated anaplastic large cell lymphoma. Haematologica. 2020 May 15. [Epub ahead of print].
12. World Health Organization classification of lymphoid neoplasms. Nat Rev Clin Oncol. 2016;13:1659–1669.
13. Oishi N, Brody GS, Ketterling RP, et al. Genetic subtyping of breast implant-associated anaplastic large cell lymphoma. Blood. 2018;132:544–547.
14. Blumberg P, Thomason E, Ryland GL, et al. Frequent activating STAT3 mutations and novel recurrent genomic abnormalities detected in breast implant-associated anaplastic large cell lymphoma. Oncotarget. 2018;9:36126–36136.
15. 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;32:216–230.
16. Taylor CR, Siddiqi IN, Brody GS. Anaplastic large cell lymphoma occurring in association with breast implants: review of pathologic and immunohistochemical features in 103 cases. Appl Immunohistochem Mol Morphol. 2013;21:13–20.
17. Clemens 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.
18. Hanson SE, Hassid VJ, Branch-Brooks C, et al. Validation of a CD30 enzyme-linked immunosorbent assay for the rapid detection of breast implant-associated anaplastic large cell lymphoma. Aesthet Surg J. 2020;40:149–153.
19. Kadin ME, Morgan J, Xu H, et al. IL-13 is produced by tumor cells in breast implant-associated anaplastic large cell lymphoma: implications for pathogenesis. Hum Pathol. 2018;78:54–62.
20. Küçük C, Jiang B, Xu X, et al. Activating mutations of STAT5B and STAT3 in lymphomas derived from γδ-T or NK cells. Nat Commun. 2015;6:6025.