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SPECIAL TOPIC

Synchronous Breast Implant–associated Anaplastic Large Cell Lymphoma and Invasive Carcinoma: Genomic Profiling and Management Implications

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SUMMARY: A 59-year-old woman with a history of cosmetic implants developed ipsilateral synchronous breast implant–associated anaplastic large cell lymphoma (BIA-ALCL) and invasive ductal carcinoma in the left breast. Each tumor was subjected to next-generation sequencing, and separate analyses revealed mutually exclusive aberrations: an activating *STAT3* mutation in the lymphoma and a *PIK3CA* in-frame deletion in the carcinoma. The patient was treated with removal of implants, capsulectomy, partial mastectomy, sentinel node biopsy, radiotherapy, and endocrine therapy with no evidence of recurrence for 1 year. This case illustrates the importance of obtaining thorough evaluation for concomitant malignancies in the breast at the time of diagnosis of BIA-ALCL. Herein, we review the current recommendations for evaluation and management of BIA-ALCL. *(Plast Reconstr Surg Glob Open 2019;7:e2188; doi: 10.1097/GOX.0000000000002188; Published online 4 April 2019.)*

CASE REPORT

The patient is a 59-year-old woman who had cosmetic augmentation with Allergan 468 textured saline implants at age 41. In subsequent years, she underwent routine screening mammography according to recommended guidelines. Eighteen years after implant augmentation, she developed swelling of the left breast. Ultrasonography identified a periprosthetic fluid collection; aspiration of the seroma produced murky, yellow fluid. Cytologic analysis showed an atypical lymphocyte proliferation positive for CD3, CD30, and CD4, and negative for anaplastic lymphoma kinase (ALK), CD2, and CD5 by immunohistochemistry. Whole body positron emission tomography with computed tomography (PET-CT) showed a nonavid seroma surrounding a deflated left breast implant, but no masses or other suspicious findings (Fig. 1A). Her previous screening mammogram 6 months earlier had been negative. She underwent implant removal with capsulectomy which showed clusters of atypical pleomorphic cells with prominent nucleoli and horseshoe-shaped nuclei (hallmark cells) below the surface of the capsule with focal early invasion (Fig. 1B). The atypical cells showed positive immunohistochemical staining of CD30 (**see figure, Supplemental Digital Content 1,** which displays the BIA-ALCL was positive for CD30 by immunohistochemistry, ***http://links.lww.com/PRSGO/B33***), CD3 (subset weak), CD4, T-cell intracytoplasmic antigen (TIA-1, subset), and epithelial membrane antigen (EMA), and were negative for CD2, CD5, CD7, CD8, ALK, CD15, B-cell markers, and Epstein-Barr virus (EBV)-encoded RNA in situ hybridization, consistent with ALK-negative breast implant–associated anaplastic large cell lymphoma (BIA-ALCL). The clinicopathologic stage was pT2.[1]

Six months later she underwent screening mammography prior to the planned implant replacement and was found to have a spiculated mass in the upper outer left breast (Fig. 2A); this was not seen on the prior mammogram 12 months earlier. Core needle biopsy showed invasive ductal carcinoma (IDC), which was estrogen receptor positive, progesterone receptor positive, and HER2 negative. Diagnosed within 6 months of one another, the patient's 2 tumors may be considered synchronous.[2] With a family history of leukemia and cancer of the colon, lung,

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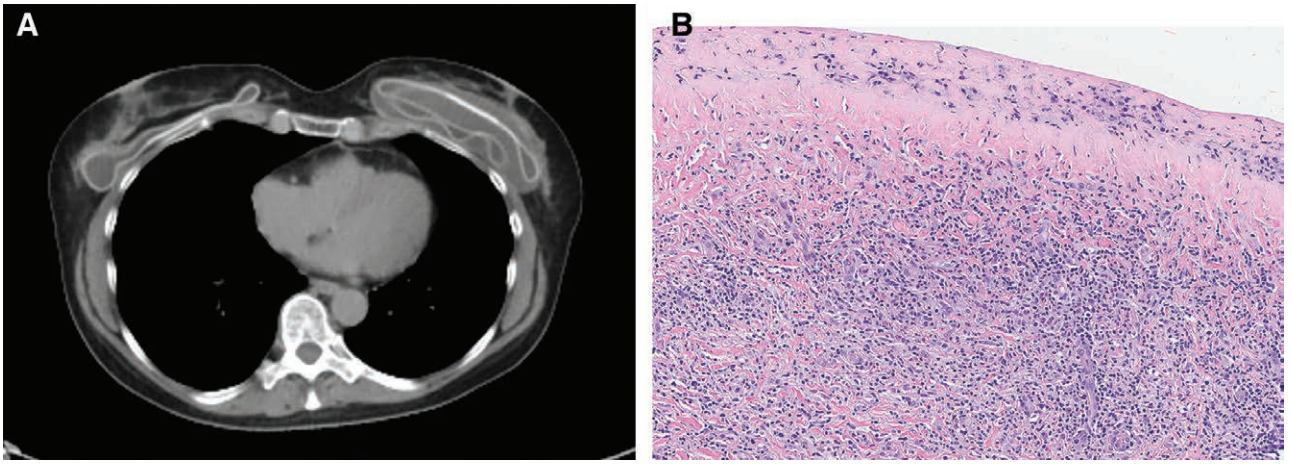

Fig. 1 . Breast implant-associated anaplastic large cell lymphoma. A, CT imaging showed seroma surrounding deflated left breast implant. B, Hematoxylin and eosin–stained section of capsulectomy specimen with BIA-ALCL underlying the surface.

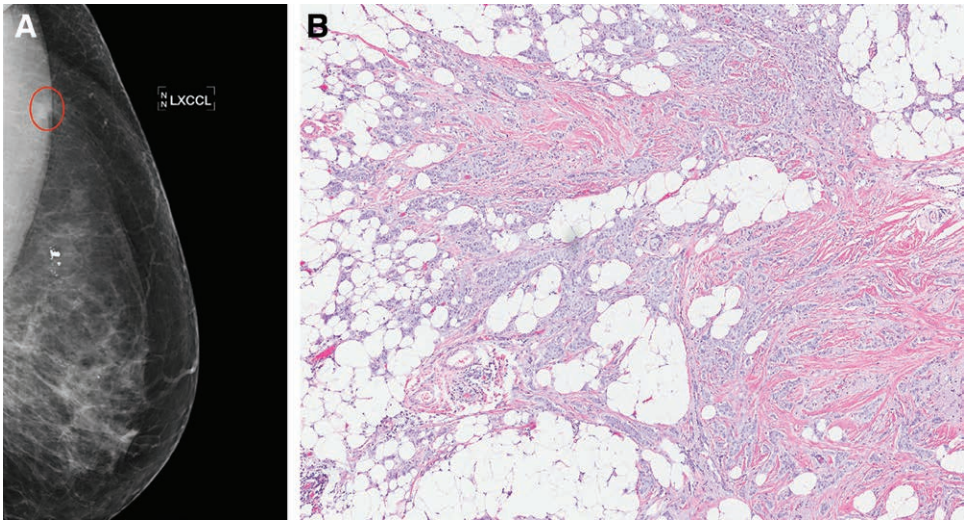

Fig. 2. Invasive ductal carcinoma. A, Left diagnostic mammogram showing spiculated mass (circled) on craniocaudal view. B, Hematoxylin and eosin–stained section of partial mastectomy specimen with grade 2 IDC.

and esophagus, the patient underwent germline testing with a panel of 85 breast cancer-associated genes (Invitae, San Francisco, Calif.). No pathogenic or likely pathogenic germline aberrations were detected. She then underwent left partial mastectomy, sentinel lymph node biopsy, and bilateral oncoplastic mammoplasty. Pathology showed a 1.2-cm grade 2 IDC (Fig. 2B) with negative margins, 1 intramammary lymph node with micrometastatic carcinoma, and 2 negative sentinel nodes. The pathologic stage was pT1cN1mi(sn). Oncotype Dx testing of the IDC showed a low-risk recurrence score of 18. She was treated with hypofractionated whole breast radiotherapy with tangents to the axilla, and an aromatase inhibitor.

After obtaining informed consent, we used capture-based next-generation sequencing to more comprehensively characterize both the BIA-ALCL and the IDC. This assay (UCSF500 panel) targets the coding regions of 479 cancer-related genes, select introns from 41 genes, and the *TERT* promoter (**see table, Supplemental Digital Content 2**, which displays 479 cancer-related genes on the UCSF500 panel, ***http://links.lww.com/PRSGO/B34***).

Sequencing libraries were prepared from genomic DNA of tumor and matched normal formalin-fixed, paraffin-embedded tissue extracted from unstained sections. Target enrichment was performed by hybrid capture using a custom oligonucleotide library. Sequencing was performed on a HiSeq 2500 (Illumina, San Diego, Calif.). In the BIA-ALCL, a pathogenic missense mutation in *STAT3* (p.S614R) was identified (Fig. 3A and B). Confirmatory immunohistochemistry for phospho-STAT3 (Tyr705) highlighted the tumor cells (Fig. 3C). Copy number analysis showed chromosomal gains in 12p and 21q. Analysis of the IDC showed a likely pathogenic and activating in-frame deletion in *PIK3CA* (p.G106_R108del) (Fig. 4A and B). Numerous partial chromosomal gains and losses were identified; no focal amplifications or deep deletions were

detected. No pathogenic or likely pathogenic germline alterations were seen in the normal tissue. No somatic variants were shared between the two malignancies (**see table, Supplemental Digital Content 3**, which displays all somatic variants detected in the BIA-ALCL, ***http://links.lww.com/PRSGO/B35***; and **see table, Supplemental Digital Content 4**, which displays all somatic variants detected in the IDC, ***http://links.lww.com/PRSGO/B36***).

The mean target sequencing coverage was 68 and 711 unique reads per target interval for the BIA-ALCL and IDC, respectively.

EVALUATION AND MANAGEMENT OF BIA-ALCL

ALCL is a rare entity, characterized by CD30 positivity and classified by clinical presentation (systemic versus cutaneous) and the presence or absence of rearrangements of *ALK*.[4] In 1997, the first case of ALCL occurring in the periprosthetic tissue surrounding a breast implant was reported.[5] Since then, numerous reports of a new clinicopathologic entity, BIA-ALCL, have been published, with approximately 500 cases reported worldwide.[6,7] Although the etiology is unclear, BIA-ALCL is associated with textured implants and the presence of bacterial biofilm.[8] The typical presenting symptom is a late periprosthetic seroma, but the detection of a mass, capsular contracture, axillary lymphadenopathy, B-type symptoms, and skin lesions have also been noted.[6] Although the systemic form of ALK-negative ALCL typically has a poor prognosis, BIA-ALCL confined to the periprosthetic fluid appears to have favorable outcomes in most cases.[7]

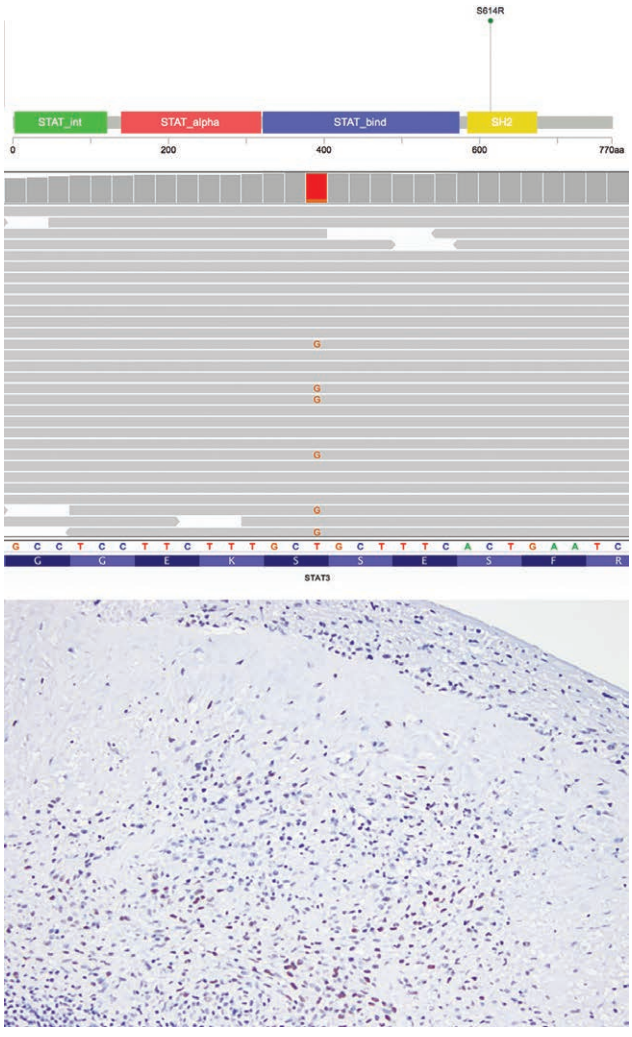

Fig. 3. STAT3 alteration in breast implant-associated anaplastic large cell lymphoma. A, Lollipop plot and (B) Integrative Genomics Viewer depiction of *STAT3* p.S614R variant in BIA-ALCL. Lollipop plot was modified from cBioPortal.[3] C, The BIA-ALCL was positive for phospho-STAT3 (Tyr705) by immunohistochemistry.

Recent work has begun to characterize the molecular landscape of BIA-ALCL. The largest series to date showed that all cases of BIA-ALCL were negative for the alterations reported in other ALCL subtypes, namely, rearrangements in *ALK*, *DUSP22*, and *TP63*.[9] Instead, alterations in JAK-STAT genes are relatively common (27% of cases), and the *STAT3* missense variant we identified (p.S614R) has been previously reported in 3 other cases of BIA-ALCL and in the TLBR1 BIA-ALCL cell line.[9–12] Located in the SH2 domain, this gain-of-function mutation results in enhanced transcriptional activity of *STAT3*. Also reported in systemic ALK-negative and cutaneous ALCL, *STAT3* mutations are increased in malignancies associated with persistent immune stimulation.[7,11,13] Although the pathogenesis of BIA-ALCL is unknown, the presence of inflammatory cytokines such as IL-6 and IL-13 suggests a component of allergy and aberrant immune response in its development.[7,13]

Profiling of the synchronous IDC showed no common genetic aberrations with the BIA-ALCL, suggesting different mechanisms of pathogenesis. The IDC harbored a *PIK3CA* alteration, which is seen in approximately 30% of breast cancers, and more commonly in estrogen receptor-positive tumors.[14] Aberrant PIK3CA activation drives cellular proliferation and survival, and gain-of-function mutations are able to transform normal breast epithelial cells to carcinoma. Currently, trials of PI3K inhibitors for advanced/metastatic breast cancer are ongoing.[15] Interestingly, *PIK3CA*-mutant breast cancer mouse models show upregulated STAT3 signaling compared to other mouse models of breast carcinogenesis, and inhibition of STAT3 sensitizes tumor cells to PI3K inhibitors.[16]

Awareness of the initial evaluation and management of BIA-ALCL, and the possibility of discovering concomitant malignancies are critical for plastic surgeons. Although early treatment of BIA-ALCL was variable, efforts by the Food and Drug Administration (FDA), implant manufacturers, national professional organizations, and physician scientists across many specialties have led to multidisciplinary consensus guidelines to aid in diagnosis, treatment, and tracking of this disease. In 2017, the National Comprehensive Cancer Network gathered medical, surgical, and radiation oncologists and plastic surgeons to create guidelines to better standardize the management of BIA-ALCL.

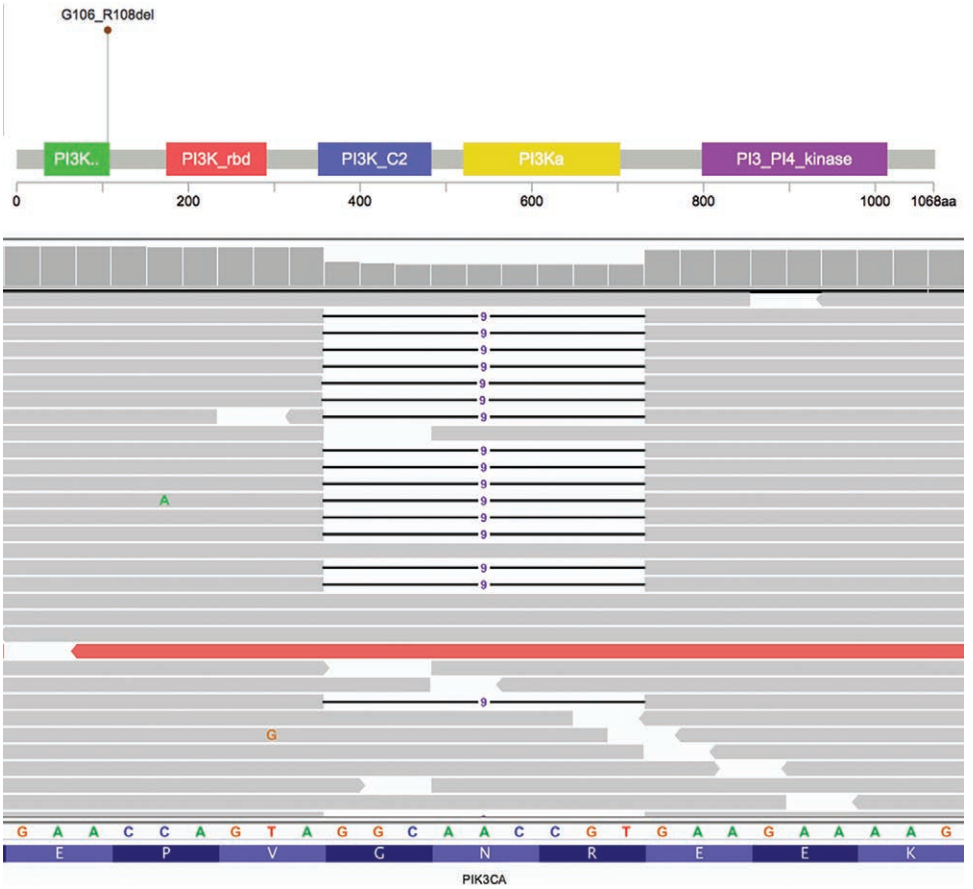

Fig. 4. PIK3CA alteration in invasive ductal carcinoma. A, Lollipop plot and (B) Integrative Genomics Viewer depiction of *PIK3CA* p.G106_R108del variant in IDC. Lollipop plot was modified from cBioPortal.[3]

Preoperative Consultation

The initial consultation with a patient considering prosthetic breast reconstruction or augmentation should include a discussion about the risk of BIA-ALCL.[17] The risk is thought to be equal between reconstructive and cosmetic patients and has variable incidence based on geographic location.[18,19] Currently, the lifetime risk for developing BIA-ALCL in women with textured implants is between 1 in 4,000 and 30,000 in the United States, but may be as high as 1 in 1,000 in Australia.[20] This risk is much lower than the background risk of breast cancer in women, estimated at 12.4%, or the risk of recurrence in patients who have had a mastectomy.[21]

Intraoperative Decision Making

In both patients undergoing augmentation mammoplasty and patients undergoing prosthetic breast reconstruction, the risk of subsequently developing BIA-ALCL appears to be similar.[1] Currently, no data on implant location (submuscular or prepectoral) exist to dictate whether the plane of implant placement affects risk.[22] Of the over 500 cases reported to date, only patients who have had a textured implant or expander have been confirmed to develop BIA-ALCL.[23] Therefore, consideration should be paid to whether the benefits of implant texturing are worth the increased risk of developing this rare disease. As inflammation possibly from bacterial contamination at the time of surgery is thought to play a role in the development of BIA-ALCL, a 14-point intraoperative plan has been suggested which outlines various steps throughout a case that may help reduce the risk of contamination.[24]

Standard Postoperative Care

After routine postoperative care, there are no specific guidelines for routine monitoring to detect BIA-ALCL. Existing FDA recommendations suggest that patients with silicone implants undergo screening for silent rupture with magnetic resonance imaging of the breast at 3 years after placement, followed by every 2 years.[25] Mammography should be obtained for breast cancer screening or surveillance based on prior oncologic history.[26] Patients should receive education about the natural history of BIA-ALCL, typically presenting as a late-onset fluid collection, asymmetric swelling, mass, or skin changes any time after 1 year from implant placement.[27,28] Although more common causes such as trauma or infection can result in these changes, and the absolute risk of ALCL in patients with these findings is low, patients should be instructed to reach out to their plastic surgeon for comprehensive evaluation.

Patients presenting for evaluation of suspected BIA-ALCL should have a thorough surgical and oncologic his-

tory obtained with the dates and specifics of procedures and treatments including what type of implant was placed. Clinical history of the changes that prompted evaluation should also be addressed. Physical exam should evaluate the chest for implant asymmetry, malposition, presence of a clinically palpable effusion or mass, skin changes, and regional adenopathy. Any abnormality should prompt subsequent imaging.[29]

Imaging Studies

The initial diagnostic test of choice is breast ultrasound to evaluate for periprosthetic fluid collection, mass, or regional adenopathy.[26,28–30] The sensitivity of detection of a fluid collection in a patient with BIA-ALCL is 84% based on one retrospective study, and lower for detection of a mass at 46%. The specificity for effusion and mass detection were 75% and 100%, respectively.[31] If an effusion is found, fluid should be aspirated and sent for evaluation. At least 20 ml of fluid should be sampled if possible, but volumes of 50–100 ml are ideal to decrease the risk of false negative or indeterminate findings.[26] Fluid should be sent for culture and Gram stain, cell block cytology, immunohistochemistry, and flow cytometry.[28–30] Alerting the pathologist that BIA-ALCL is a diagnostic consideration is important to ensure appropriate tests (including comprehensive flow cytometric markers) are done.

If ultrasound evaluation is inconclusive, breast magnetic resonance imaging can be considered because it is the next most sensitive imaging test for effusion.[31] If a mass is found, biopsy should be performed. CT and mammography lack sufficient sensitivity and specificity to recommend their use in the workup of BIA-ALCL. However, PET should be considered in selected cases to provide information about the extent of local disease and the presence of metastatic disease once diagnosis of BIA-ALCL is made.[26,29–31] Current guidelines for the workup of BIA-ALCL do not include the use of mammography in the preoperative evaluation.[30] However, the diagnosis of ipsilateral IDC 6 months later in this patient suggests that thorough diagnostic breast imaging including mammography should be obtained prior to breast surgery. Although impossible to know whether mammography at the time of BIA-ALCL diagnosis would have identified the IDC, PET/CT is not a reliable replacement for thorough diagnostic workup of the breast, as the sensitivity for detection of primary breast tumors is reported to be only 68% for tumors less than 2 cm in size.[32]

Consultations

Patients with negative findings for lymphoma on initial workup may be appropriately managed by a plastic surgeon for management of seroma or infection. However, an indeterminate diagnosis on initial pathology warrants additional workup. This may include having the slides sent to an outside pathologist or referral to a tertiary care center, either of whom with experience in treatment of BIA-ALCL.[30] A diagnosis of lymphoma should result in referral to a center with a multidisciplinary team of medical, surgical, and radiation oncologists, plastic surgeons, and hematopathologists.[1,6]

Surgery

Removal of the implant and total capsulectomy remains the mainstay of therapy for BIA-ALCL and is curative in a majority of cases.[1,31] Consideration should be given to having a surgical oncologist present at the time of surgery, especially with extensive disease or need for lymph node surgery. Sentinel lymph node biopsy is not routinely recommended given the variable drainage patterns of the large breast implant capsule, but the removal of suspicious lymph nodes at the time of implant removal is recommended.[1,26,27,30] Removal of the contralateral breast implant at the time of surgery is not mandated by guidelines, but reports of occult contralateral BIA-ALCL in patients undergoing implant removal with preoperatively diagnosed lymphoma should be discussed with patients.[33] There are sparse studies evaluating the optimal timing of implant replacement following removal for BIA-ALCL. Early data suggest immediate replacement is safe and has some advantages over delayed replacement, but surgeons should choose smooth implants and treat every patient on a case-by-case basis.[33]

Adjuvant Therapy

For patients with BIA-ALCL confined to the capsule or implant and who complete surgical resection with no residual disease, adjuvant therapy is not currently recommended. For patients with evidence of lymphoma extending beyond the implant capsule or residual disease in the breast due to inability to completely resect the tumor, adjuvant therapy is indicated.[1,29,33] Adjuvant therapy decisions should be made in a multidisciplinary setting on a case-by-case basis, but in general radiation therapy (24–36 Gy) is advocated for residual local disease in patients without a history of prior chest wall radiation, and chemotherapy is advocated for patients with positive lymph nodes or evidence of spread to distant sites. The most common chemotherapeutic agents or regimens include brentuximab vedotin, a monoclonal antibody targeting CD30 with individual case reports demonstrating efficacy in BIA-ALCL, or chemotherapy combinations recommended for peripheral T-cell lymphomas such as cyclophosphamide, doxorubicin, vincristine, and prednisone or variations thereof.[26,34–36]

Follow-up

After primary management, National Comprehensive Cancer Network guidelines recommend surveillance for recurrence of BIA-ALCL for a minimum of 2 years with physical examination and, if indicated, CT chest/abdomen/pelvis or whole body PET/CT every 6 months, after which patients should resume routine breast cancer screening.[30] The development of recurrent clinical findings in the breast at any point should prompt referral back to their plastic surgeon, and warrants repeat diagnostic imaging.

Reporting

All cases of BIA-ALCL should be reported to the FDA through their MedWatch adverse events reporting program. In addition, the Plastic Surgery Foundation has set

up a registry called Patient Registry and Outcomes For breast Implants and ALCL etiology and Epidemiology (PROFILE) that helps track and better understand the causes and treatments of BIA-ALCL.[19]

CONCLUSIONS

To the best of our knowledge, this is the first report of a patient with synchronous BIA-ALCL and IDC in the same breast. This case illustrates the importance of evaluating for additional malignancies in the breast when a diagnosis of BIA-ALCL is made; diagnostic mammogram at the time of workup of BIA-ALCL may be a useful adjunct to ultrasound and PET/CT to identify additional breast malignancies prior to surgery. Future studies may identify susceptibility factors and further elucidate the potential relationship between BIA-ALCL and IDC.

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