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Recurrent Systemic Anaplastic Lymphoma Kinase–Negative Anaplastic Large Cell Lymphoma Presenting as a Breast Implant–Associated Lesion

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Summary: A woman aged 48 years presented with fevers, chills, weight loss, and night sweats. She had significant lymphadenopathy of the left neck as well as the left axilla. Her history was significant for bilateral breast augmentation with textured silicone implants more than 25 years ago. Excisional biopsy of a cervical lymph node revealed large, atypical cells positive for CD4 and CD30 and negative for Epstein–Barr virus–encoded ribonucleic acid, CD2, CD3, CD5, CD7, CD8, CD15, CD20, pan-keratin, S100, anaplastic lymphoma kinase (ALK), and paired box 5. These findings were consistent with Ann Arbor stage IIIB ALK– anaplastic large cell lymphoma (ALCL). The patient was started on 6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone. She initially had no signs or symptoms of breast involvement; however, after developing seroma during the clinical course, the patient underwent capsulectomy and removal of the intact, textured silicone implants. Pathological evaluation demonstrated ALK– ALCL in the left breast capsule with cells displaying a significant degree of pleomorphism with binucleated forms and numerous mitoses. Fluorescence in situ hybridization confirmed the tumor was negative for t(2;5). She presented 8 weeks later showing evidence of recurrent systemic disease.

Background

Breast implant–associated anaplastic large cell lymphoma (ALCL) is a rare T-cell neoplasm typically presenting in women as a mass or late seroma in the breast implant capsule.[1,2] Textured silicone implants have been associated with an increased risk for the development of ALCL, which may occur as a reactive process involving the fibrous capsule.[3-6] Breast implant–ALCL is histologically and molecularly indistinguishable from anaplastic lymphoma kinase (ALK)–negative ALCL.[7,8]

In 2011, the US Food and Drug Administration reported a possible association between breast implants and ALCL.[3] To date, approximately 173 cases have been published in the English literature.[9] The estimated yearly incidence of primary ALCL of the breast is 1 per 100,000,000, and the estimated 5-year overall survival rate is 92%.[10] By contrast, systemic ALK– ALCL accounts for 2% to 3% of all non-Hodgkin lymphomas and has a poorer prognosis (5-year overall survival rate of 20%–50%).[11,12] More than 80% of patients with breast implant–ALCL present with stage 1 disease.[10] Most patients with breast implant–ALCL have small clusters of neoplastic cells lining the fibrous capsule within serous effusions, whereas some patients present with a tumor mass within or beyond the capsule.

Although it may disseminate, the disease typically remains indolent such that the distinction between de novo systemic ALK– ALCL and breast implant–ALCL has prognostic implications. Current treatment for breast implant–ALCL restricted to the breast implant capsule consists of bilateral implant removal and capsulectomy with subsequent close follow-up.[9,10] In cases of disseminated disease, chemotherapy, radiation, bone marrow transplant, or all 3 options can be considered. It is important for health care professionals to be aware of the association between breast implants and ALK– ALCL, the ways in which the disease may present, and, as illustrated in this case report, the importance of differentiating between ALCL types.

Case Report

Clinical History

A woman 48 years of age presented with fevers, night sweats, and weight loss accompanied by masses in

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the left neck and left axilla. Excisional biopsy of a cervical lymph node was consistent with ALK– ALCL. Bone marrow biopsy was performed and no involvement was noted. Positron emission tomography showed hypermetabolic left cervical lymphadenopathy, left axillary lymphadenopathy, and splenic hilar lymphadenopathy without contralateral involvement, consistent with Ann Arbor stage 3B ALK– ALCL. The patient was without signs, symptoms, or radiographic evidence of breast involvement.

Her history was significant for bilateral breast augmentation with textured silicone breast implants at the age of 21 years via a transaxillary approach. Thirteen years after implantation, she had left capsular contracture and underwent left capsulectomy and exchange of the left breast implant via an inframammary fold approach.

The systemic ALK– ALCL was treated with 6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone, and resolution was seen at all sites of disease by positron emission tomography 1 month after her last cycle. Two months after completion of the chemotherapy, the patient reported swelling of the left breast (Fig 1). In addition to swelling and firmness, a new 10 × 4 cm erythematous area overlying the site of the prior implant incision was discovered. Ultrasonography demonstrated periimplant seroma, which was subsequently aspirated. Cytological evaluation was consistent with recurrent ALK– ALCL.[13,14]

The patient underwent bilateral total capsulectomy and removal of the intact, textured silicone implants (see Fig 1). A large fluid collection was encountered in the left breast, and approximately 200 cc of fluid was collected for cytology. No palpable masses were appreciated. Scarring extending toward the axilla on the left breast was noted and was believed to have been a result of the transaxillary approach used when placing the implants. The postoperative course was without complications.

Positron emission tomography performed 8 weeks later showed evidence of recurrent bilateral systemic disease, and multiple new hypermetabolic lesions were seen above and below the diaphragm. Biopsy of the right axillary lymph node confirmed recurrent ALK– ALCL. The patient underwent salvage chemotherapy with 2 cycles of etoposide, methylprednisolone, cytarabine, and cisplatin but did not achieve remission. The patient achieved complete remission following 3 cycles of anti-CD30 therapy with brentuximab vedotin and was scheduled to receive an allogeneic hematopoietic stem cell transplant.

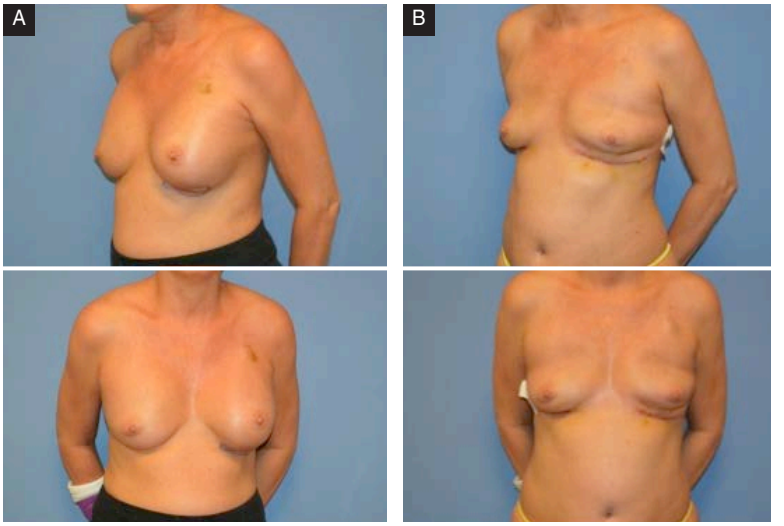

Fig 1A–B. — Preoperative and postoperative imaging. (A) These images show the preoperative presentation with notable left breast swelling. (B) These images demonstrate the appearance of the left breast following implant removal and capsulectomy.

Pathological Findings

Initial excisional biopsy of a cervical lymph node revealed cells positive for CD4 and CD30 and negative for Epstein–Barr virus–encoded ribonucleic acid, CD2, CD3, CD5, CD7, CD8, CD15, CD20, pankeratin, S100, ALK, and paired box 5, consistent with ALK– ALCL. The capsulectomy specimen had tumor involvement that consisted of large, single, scant CD30-positive tumor cells along the inner surface of the fibrous capsule. Cytologically, the malignant cells were large and had abundant cytoplasm, mostly eccentric nuclei, and multiple prominent nucleoli. The cells displayed a significant degree of pleomorphism with binucleated forms and numerous mitoses (Fig 2A–C). Fluorescence in situ hybridization confirmed the tumor was negative for t(2;5) (Fig 2D).

Discussion

This report represents a notable case of systemic ALK– ALCL in a patient with breast implants. It underscores the importance of a thorough clinical examination and, if warranted, pathological evaluation of the breasts in women with a history of breast implants and ALK– ALCL. The patient initially presented with systemic disease localized to the left axilla, left neck, and splenic hilum, but she did not have breast signs or symptoms. At the time of progression, the disease mimicked breast implant–ALCL of the left breast with isolated unilateral, effusion-only disease without a breast mass. It is prognostically important to establish whether breast involvement is secondary to systemic ALK– ALCL or a truly implant-associated process; however, doing so is not possible on morphological or immunohistochemical grounds alone. Tissue collected at diagnosis from an outside institution was inadequate to perform T-cell receptor rearrange-

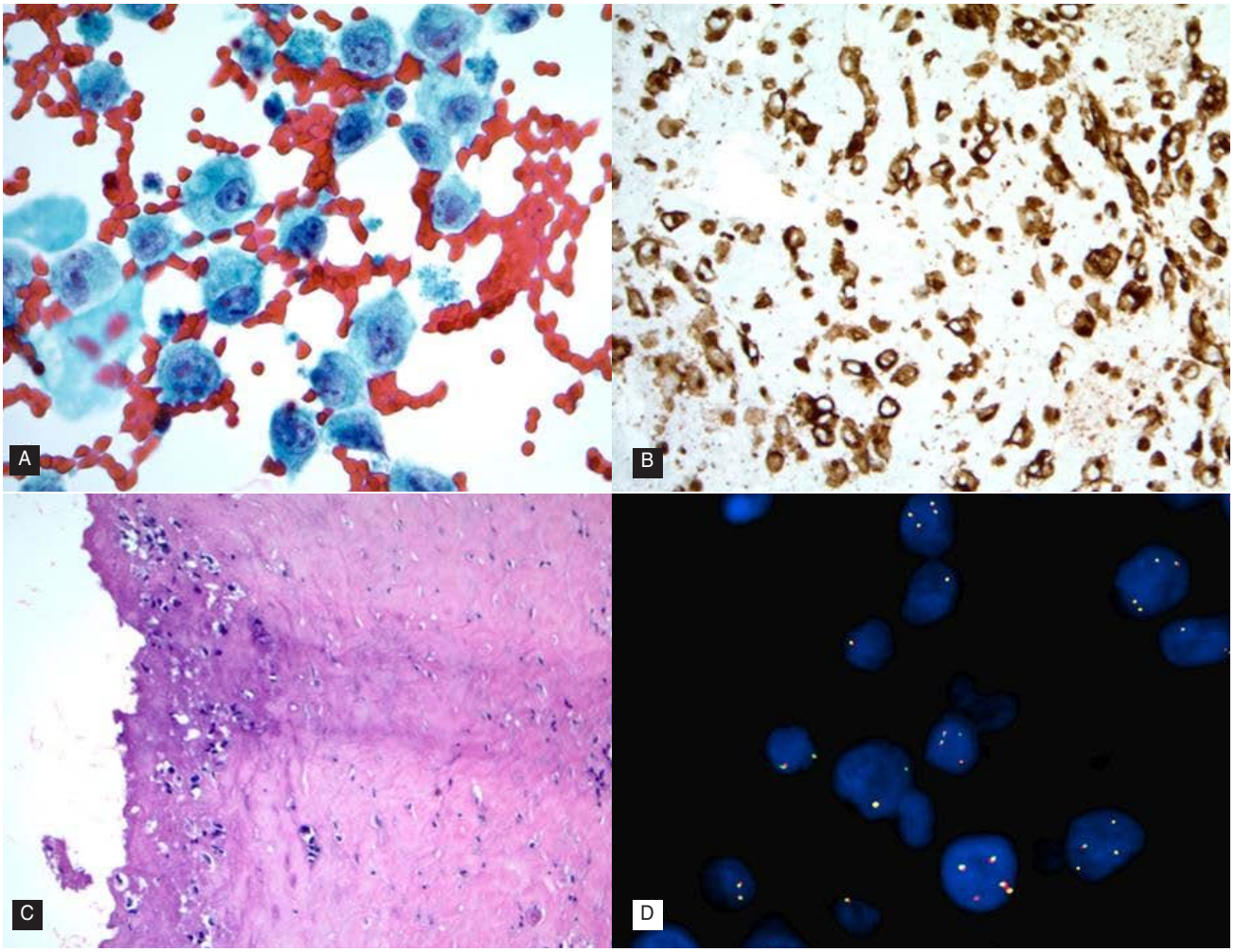

Fig 2A–D. — (A) Fluid cytology reveals large, highly pleomorphic cells with abundant foamy cytoplasm and eccentric nuclei with several prominent nucleoli (Papanicolaou stain, × 40). (B) Histological section of the capsule showing involvement in the inner surface by malignant cells (hematoxylin and eosin, × 10). (C) Anaplastic malignant cells are strongly positive for CD30 immunohistochemistry (× 20). (D) Fluorescence in situ hybridization is negative for t(2;5). Panel D photographed by Dr Kenian Liu.

ment analysis, but tissue obtained via both the left capsulectomy and subsequent axillary node biopsy was confirmed to be of the same clonal origin. This finding proved that the systemic disease at relapse was of the same origin of breast implant–ALCL and strongly suggested that the initial systemic ALCL was not a separate clonal entity from the breast implant–ALCL in this case.

The possible explanations for the origin of the patient's disease are either that the tumor systematically arose de novo and secondarily tracked to the breast where it progressed, or that the disease originated in the breast but remained undetectable at that site until shortly after initial chemotherapy, which is when breast involvement was noted. It is possible that the breast implant capsule favored the spread of disease to that site; however, based on the unilateral localization of nodal disease in the axilla and neck at presentation, we believe the likely origin of the tumor was the left breast implant capsule.

Conclusions

This case has implications for health care professionals given the statistical link between anaplastic large cell lymphoma (ALCL) and breast implants. Our case illustrates the importance of a thorough breast examination and low threshold for mammography or ultrasonography in women with breast implants presenting with systemic anaplastic lymphoma kinase (ALK)–negative ALCL. In our opinion, bilateral capsulectomies should be considered as treatment for all patients with breast implant–ALCL. In addition, ALK– ALCL associated with breast implants can aggressively behave and become resistant to chemotherapy. Health care professionals should also consider brentuximab as a treatment option for patients with CD30-positive, breast implant–ALCL.

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