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LETTER TO THE EDITOR
BREAST IMPLANT-ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA (BI-ALCL)

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Lymphomas are a heterogeneous group of malignant neoplasms constituted by lymphoid cells[1]. The occurrence of lymphomas in breast is exceeding rare, but several histotypes have been occasionally reported[2]. Breast implant-associated anaplastic large cell lymphoma (BI-ALCL) is a recently defined non-Hodgkin's T-cell lymphoma developing in late peri-implant breast seroma. Although its exact incidence is not perfectly defined, BI-ALCL seems to be very rare, representing 2 to 3% of all non-Hodgkin's lymphomas in adults and 0.5% of all breast neoplasms[3]. Although the pathogenesis of BI-ALCL is largely unknown, the constitutive activation of the JAK/STAT3 pathway seems to play an important role, similarly to other ALK-negative anaplastic T-cell lymphomas[4]. Indeed, the missense variant (p.S614R), a gain-of-function mutation of the SH2 domain mediating STAT3 dimerization, has been recently described in BI-ALCL and in other lymphoid proliferations including angioimmunoblastic T cell lymphomas, chronic lymphoproliferative disorders of natural killer cells, and T-cell large granular lymphocyte leukaemias. A frameshift deletion causing a premature stop codon in SOCS1 (p.P83Rfs*20), a negative feedback regulator of the JAK/STAT3 pathway, has been detected in BI-ALCL. Furthermore, additional somatic events seem to be represented by a missense mutation of TP53 (p.D259Y) affecting the DNA binding domain and a nonsense mutation in DNMT3A (p.W176X), a DNA methyltransferase required for genome-wide de novo methylation.

The bacterial biota is hypothesized to play a role in the pathogenesis of BI-ALCL, similarly to other gastric and cutaneous lymphomas. Indeed, both Gram-positive and Gram-negative species may cause a proliferation of the CD4-positive cells in the biofilm interface over the capsule, particularly in case of texturized implants. A direct correlation between the lymphoma occurrence and the implant type – considering the material (silicone, saline solution, silicone/saline solution combination, polyurethane), the cover design (texturized or smooth superficies) and position – is not well defined. BI-ALCL is an indolent lymphoma and few cases have been reported showing an aggressive behavior with capsule infiltration and systemic dissemination. The more aggressive cases are characterized by infiltrative histological pattern, bilateral presentation, extracapsular tumor invasion, solid breast nodules and axillary lymph nodes involvement. In most cases, the neoplastic cells are present only in seroma fluid, or are discontinuously arranged in the inner side of the fibrous capsule. Rarely, in more advanced phases, the cells may massively infiltrate the capsule and eventually the surrounding breast parenchyma. Currently, the optimal treatment of BI-ALCL is controversial and not standardized. Bilateral surgical removal of the capsule implants is recommended and also new treatments as Brentuximab, an anti-CD30 antibody-drug conjugate, can be helpful in advanced and aggressive cases.

The diagnosis of BI-ALCL may be challenging and requires the correct management of the sample. Cytology allows a correct differential diagnosis between BI-ALCL and reactive inflammatory seroma[5]. Mostly, the recognition of BI-ALCL on cytological samples is essential to avoid a delay in removing the capsule and implant that could lead to a dissemination of the disease with involvement of the breast-parenchyma. The collection of a minimum of 10 to 50 mL of the effusion fluid surrounding the affected implant, is necessary for preparation of cytopathology smears. After cytocentrifugation and filtration, air-dried smears are stained with Wright-Giemsa

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or other Romanowsky-type stains. The preparation of a cell block is also useful in order to obtain hematoxylin/eosin stained slides for immunohistochemical analysis and molecular genetic studies. The stained smears show large pleomorphic cells – that are several times larger than a normal small lymphocyte – with irregular nuclei, large prominent nucleoli, moderate cytoplasm and a conspicuous mitotic activity. "Hallmark cells", a subpopulation of cells with horseshoe or kidney-shaped nuclei, seen in other forms of ALCL, are also present. The immunohistochemical panel of BI-ALCL – like other forms of ALK-negative ALCL – shows cells uniformly and strongly positive for CD30 and negative for ALK, a variable positivity for epithelial membrane antigen and an incomplete expression of pan-T-cell antigens. If ALK immunohistochemistry can be adequately interpreted, FISH for ALK rearrangements is not necessary while Polymerase Chain Reaction (PCR) is useful in the evaluation of T-cell receptor (TCR) gene rearrangements, which have been identified in nearly all BI-ALCLs reported[6].

When capsulectomy is performed, the ideal resection includes the intact capsule containing the implant, surrounding effusion and any associated masses. The effusion is saved for cytologic examination, the implant is carefully removed and the capsule and any floating or attached material to the implant are submitted for histologic evaluation.

The evolution of the disease, particularly when lymphoma extends to the regional lymph nodes, chest wall or distant sites, is still poorly understood but the cytologic evaluation of the effusion plays an essential role for a reliable diagnosis, management and treatment of BI-ALCL.

Conflict of Interests:
The authors declare that they have no conflict of interest.

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