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Breast implant-associated anaplastic large cell lymphoma

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Abstract

Review on Breast implant-associated anaplastic large cell lymphoma with clinics and the genes involved

Keywords
Breast implant-associated anaplastic large cell lymphoma; Seroma-associated anaplastic large cell lymphoma

Identity

Other names
Seroma-associated anaplastic large cell lymphoma

Clinics and pathology

Disease

Breast implant-associated anaplastic large cell lymphoma (BI-ALCL) is a new provisional entity described in the 2017 revision of the World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues (Swerdlow SH et al., 2016). This disorder represents an uncommon form of slow-growing T-cell lymphoma where breast implants play a leading role in the lymphomagenesis. For its diagnosis a high index of suspicion is warranted. The most common clinical presentation is an effusion around the implant, and less common as a tumor mass. (Miranda RN et al., 2014) Imaging studies, ultrasound specifically, will help the clinician diagnose this malignancy (Adrada BE, 2014). Further tests are necessary to determinate the histologic and immunophenotypic features, which are similar to other ALK-negative anaplastic large cell lymphomas (ALCLs). The vast majority of malignant cells are CD30 positive and ALK-negative (Quesada AE et al., 2019). Surgery represents the optimal approach to the disease, reaching excellent results and high rates of overall survival (OS). Chemotherapy is reserved for systemic cases, and anthracycline-based regimens are preferred (Clemens MW, Horwitz SM, 2017).

Phenotype/cell stem origin

Immunophenotype is similar to the cell expression of systemic ALK-negative ALCLs. Thus is characterized by a strong positivity for CD30 and negativity for ALK. Several markers like CD43, CD45, CD4, TIA-1, granzyme B and EMA are frequently expressed; whereas CD3 and CD8 expression are less prevalent. Epsetin-Barr virus small-encoded RNA is constantly negative, like CD1a, cyclin D1 and TdT (Quesada AE et al., 2019).

Etiology

Pathogenesis is not clearly established, however, several mechanisms have been theorized based on chronic antigenic stimulation (Laurent C et al., 2018). This pathway triggers the recruitment, expansion, and proliferation of T cells leading to clonality and malignant transformation (Roden AC et al., 2008). Local inflammation and fibrosis caused by the silicone and its degradation products sustain T-cell proliferation (Bizjak M et al., 2015). Microbiome studies have demonstrated a playing role of the gram-negative bacteria Ralostonia

pickettii, stimulating Th1 cells by the release of cytokines (Hu H et al., 2016). BI-ALCL cells present a secretory profile similar to TH1/Th17 cells and are dependent on microenvironment cytokines like IL2, IL10, and IL6 (De Leval L, 2019). The content of the implant (saline or silicone-filled) does not imply an increased risk of BI-ALCL (Miranda RN et al., 2014). However, the different outer shell of the implants (textured or smooth) will play a leading role in the pathogenesis. Some studies found a higher prevalence of BI-ALCL among patents with textured implants compared to smooth implants or the general population. This difference could be explained by the finding in textured implants of inflammation with a T-cell profile more frequently than in the smooth ones (Meza Britez ME et al., 2012). Activation of JAK/STAT3 signaling pathway and expression of cytotoxic molecules are also involved in the survival and proliferation of BI-ALCL cells (Lechner MG et al., 2012).

Epidemiology

Non-Hodgkin lymphomas (NHLs) involving the breast represent between 1-2% of all NHLs, mostly diffuse large B-cell lymphomas (DLBCLs) and extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (Laurent C et al., 2018). On the other hand, ALCLs represent 3% of NHLs (Talwalkar SS et al., 2008). BI-ALCL is an uncommon neoplasm; although in recent years an increase in recognition of this entity has been reported. In a meta-analysis, an incidence of fewer than 5 cases per 500,000 women with breast implants was described (Brody GS et al., 2015). The median age of diagnosis is 50 years (De Leval L, 2019)

Clinics

The median time interval from implant surgery to lymphoma diagnosis is 8-9 years. Two clinical presentations are seen. The vast majority of patients (80%) present with an effusion adjoining to the implant without extension to the breast parenchyma or distance. Necrotic and liquefied lymphoma cells are identified on the effusion (Miranda RN et al., 2014). This malignant seroma could be associated with asymmetry, pain or breast swelling. It is important to differentiate it from benign fluid collections, that could appear early after the surgery (De Leval L, 2019). Secondly, the other 20% of patients usually present a tumor mass infiltrating breast tissue with or without effusion, recognized by the patient as a continuous growth of an indurated area (Miranda RN et al., 2014). Also, a minority of patients (20%) may present with lymph node involvement, more frequent axillary in location (Ferrufino-Schmidt MC et al., 2018). BI-ALCLs do not usually present at diagnosis time with B symptoms or skin lesions (Mehta-Shah N et al., 2018). Two staging systems are routinely used. Ann Arbor staging system, being the patients divided in stage I (83%), II (10%) and III (7%) at diagnosis (Miranda RN et al., 2014). The National Comprehensive Cancer Network (NCCN) promotes the second one to determinate the degree of tumor infiltration into the capsule, a staging system proposed by the MD Anderson. Based on a T stage included in the clinical Tumor Node Metastasis (TNM) solid tumor staging system. In the latter, the patients are divided in IA (35.6%), IB (11.5%), IC (13.8%), IIA (25.3%), IIB (4.6%), III (9.2%) and IV (0-9%) (Clemens MW et al., 2016).

Diagnosis The diagnosis of BI-ALCL needs a high index of suspicion since it is a low-growth neoplasm and its most frequent clinical presentation (effusion) could be misdiagnosed as a benign seroma. The NCCN has established diagnosis and management guidelines that will help diagnosis this disease quicker (Clemens MW, Horwitz SM, 2017). An exhaustive physical examination has to be performed in case of clinical suspicion (fluid collection or masses) as well as imaging studies. In peri-prosthetic fluid collection cases, the ultrasound achieves the best results (sensitivity and specificity of 84% and 75% respectively), whereas magnetic resonance imaging (MRI), computed tomography (CT) and mammography are worse in terms of sensitivity/specificity in a retrospective study. Nevertheless, in tumor masses, PET CT achieved better results than MRI, but same as ultrasound (Adrada BE, 2014). Once diagnostic of effusion or tumor mass is reached, cytological/histological examination is necessary. Fine needle aspiration or tissue biopsy, depending on the clinical presentation, will provide the samples for immunohistochemical and histological studies guiding to BI-ALCL diagnosis.

Pathology

The histological features of BI-ALCL cells resemble systemic ALCLs ones. They are large cells with anaplastic and pleomorphic morphology, also an abundant cytoplasm is founded. The nuclei are large or oval, with prominent nucleoli and mitoses (Miranda RN et al., 2014). Hallmarks-cells encountered in all forms of ALCL are also founded on this subtype (specifically in 70% of cases). It is defined by an eccentric horseshoe- or kidney-shaped nuclei (Swerdlow SH et al., 2016).

Cytogenetics

ALK translocations or those involving DUSP22 or TP63 that characterize ALK positive large B-cell lymphomas and ALK- ALCLs respectively, have not been identified in BI-ALCLs (Oishi N et al., 2018). However, other molecular genetics findings have been reported. Based on Quesada AE et al., review, monoclonal TRG and TRB rearrangements are

carried by BI-ALCL cells (Quesada AE et al., 2019). Furthermore, activating mutations in STAT3 and JAK1 have also been described in neoplastic cells, as mentioned before being involved in the pathogenesis. (Oishi N et al., 2018)

Treatment

The treatment of choice depends on the extension of the disease. Notwithstanding, complete surgical excision, which includes: total capsulectomy and removal of the implant and any mass with negative margins; represents the optimal approach to all BI-ALCL (Clemens MW, Horwitz SM, 2017). In localized disease (Ann Arbor IE; TNM IA, IIA), the NCCN guidelines recommendation is complete surgical excision, with no strong role of sentinel lymph node biopsy or radical mastectomy. In residual localized disease or incomplete excision (also including disease with chest wall invasion), radiation therapy (24-36 Gy) following surgery is a reasonable option (Horwitz SM et al., 2018). It has been reported that 4.6% of patients may have incidental lymphoma in the contralateral breast, thus surgeons may consider the removal of the contralateral implant (Clemens MW et al., 2016). In systemic disease (Ann Arbor II-IV, TNM IIB-IV) systemic therapy is recommended by NCCN guidelines. Despite limited data, anthracycline-based chemotherapy, like cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or with the addition of etoposide (EPOCH), are usually administrated. The use of brentuximab vedotin (anti-CD30 antibody) has provided responses in systemic ALCLs, however further studies are needed in BI-ALCLs (Vaklavas C, Forero-Torres A, 2012). There is no standard guideline for reconstructive surgery, and both immediate and delayed reconstruction has been done (Mehta-Shah N et al., 2018).

Prognosis

BI-ALCLs have a better prognosis than systemic ALCL. Stage I patients have a 100% 3-year OS and 63% EFS (Adrada BE, 2014). A 5-year OS of 98.8% has been reported in patients treated with complete capsulectomy compared with those cases where it was not performed (57.2%) (Clemens MW et al., 2016). Lymph node involvement confers worse prognosis since a 5-year overall survival of 75% for those with lymph node involvement has been described, compared to a 97.9% in those without.
Equally, tumor masses affect prognosis since poor OS and progression free survival were found compared with patients without masses (Adrada BE, 2014).

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