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DLBCL type patients with FoxP3+ TILs exhibited significantly less TTP. These results suggested that TIME plays a vital role in pathogenesis, treatment, and prognosis of PTLD.

Keywords: post-transplant lymphoproliferative disorders (PTLDs).

152 JAK-STAT PATHWAY AND EPIGENETIC REGULATORS ARE CRITICAL PLAYERS IN BI-ALCL PATHOGENESIS?

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Background: Breast Implant-associated anaplastic large cell lymphoma (BI-ALCL) is a rare T-cell lymphoma arising in association with breast implant, particularly those with textured surfaces. We recently identified two histopathological BI-ALCL subtypes: in-situ and tumor-type which correlated with the seroma vs tumor mass clinical presentation, respectively. Although genetic events involving the JAK/STAT

pathway have been reported and the putative role of local chronic inflammation has been suspected, BI-ALCL pathogenesis remains elusive. To further explore potential molecular mechanisms involved in the pathobiology of these two distinct BI-ALCL subtypes, we performed a genomic characterization of 34 such cases.

Patient and Methods: Fifty-four BI-ALCL patients have been diagnosed through the *Lymphopath* network and registered in the Lymphoma Study Association Registry from 2010 to 2018. A total of 34 BI-ALCL samples have been analyzed by whole exome sequencing (WES) (n = 22 paired tumor/ germline DNA) and/or targeted next generation sequencing (NGS) (n = 24), across 406 genes to validate the findings. The average depth of sequencing was 300x for WES and 500x for targeted NGS.

Results: Fifty nine percent of cases (20/34) showed mutations in at least one member of the JAK/STAT signaling pathway. *STAT3*(38%) and *JAK1* (18%) were the most mutated genes whereas *STAT5B* (n = 1) and the negative regulators *SOCS3* (n = 2), *SOCS1* (n = 1) and *PTPN1* (n = 1) were seldom mutated. Fifteen percent of cases harbored simultaneous mutations in two genes of this pathway. *STAT3* mutations were more frequent in tumor-type than in-situ BI-ALCL (p = 0.0078). Recurrent mutations in epigenetic modifiers were seen in 70% of cases with *KMT2C* (26%), *CHD2* (15%), *CREBBP* (15%) and *KMT2D* (9%) being the most frequently mutated genes. Loss of function mutations in *TP53* (12%) have also been identified. Genomic alterations in genes involved in lymphocytes development such as *EOMES* and in *PI3K-AKT* and *MAP* cascades were also seen in 23.5%, 12% and 9% BI-ALCL cases, respectively. In addition, CNV analysis in 8 cases identified recurrent deletions on chromosomes 8q, 15p and 20. Furthermore, by this approach additional alterations in *SOCS3* (2/8), *SOCS1* (1/8), *PTPN1* (6/8) and *STAT5B* (3/8) as well as LOH in several epigenetic regulators such as *TET2* (3/8) and *HDAC8* (2/8) were seen.

Conclusions: This large series strongly reinforce the hypothesis that dysregulation of cytokine receptor signaling caused by recurrent mutations in the JAK/STAT pathway is a key event in BI-ALCL pathogenesis. Furthermore, our observation of frequent mutations in chromatin remodeling genes highlights the importance of epigenome and provides new insights into the complexity of BI-ALCL oncogenesis.

Keywords: anaplastic large cell lymphoma (ALCL); epigenetics; JAK/STAT.

153 SPECIFIC GENETIC ALTERATIONS CHARACTERIZE SEROMA- AND TUMOR-TYPE BREAST-IMPLANT ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA (BIA-ALCL) AS A DISTINCT DISEASE ENTITY

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