Abstract #27 | Poster

Genomic landscape of pediatric and adolescent Hodgkin lymphoma

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Hodgkin lymphoma (HL) is a common lymphoma of children, adolescents and adults. The rarity of Hodgkin-Reed/Sternberg (HRS) cells represents a major obstacle to elucidating pathogenic mechanism. Furthermore, all age groups have so far been analyzed collectively. We therefore used circulating cell free DNA (cfDNA) of pediatric (pHL) patients for whole exome sequencing to detect somatic pathogenic variants of this patient group. In pre-therapy cfDNA of 127 patients, we identified 69 recurrently mutated genes and 11 recurrent copy number gains (CNG). Cytokine signaling, NFKB activation and immune evasion were affected in the vast majority of cases. Further impacted biological processes were chromatin organization, with frequent inactivation of SWI/SNF complex components, G-protein coupled receptor signaling, genome stability and mRNA processing. Median tumor mutation burden (TMB) was 1.8 mutations/MB, the highest of all pediatric malignancies. Aberrant somatic hypermutation (ASH) was the major mutational process and related to occurrence of CNGs. Human herpes virus genome fragments, HHV5, HHV6 and mainly EBV, were detected in 42% of pre-therapy but only 2% of aftercare cfDNA samples. EBV fragments were present in patients with EBV+ and EBV- HRS cells, with much lower concentrations in the latter. Comparison of various patient groups revealed that ctDNA load correlated with stage and presence of B symptoms, and TMB correlated with induction therapy response. With large language model based text mining of somatic variants, we identified a patient subgroup with high prevalence of classical NFKB pathway activating mutations, higher ctDNA burden, more advanced stages and more frequent extranodal disease.