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ARRAY-BASED COMPARATIVE GENOMIC HYBRIDIZATION ANALYSIS OF AGGRESSIVE EPIDERMOTROPIC CD8+ CYTOTOXIC T-CELL LYMPHOMA (AECD8+L), EXTRANODAL NK/T NASAL TYPE LYMPHOMA (ENK/T-NT) AND BLASTIC PLASMOCYTOID DENDRITIC CELL NEOPLASIA (BPDCN).

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To better define molecular alterations involved in these proliferations, we performed an array-based high resolution comparative genomic hybridization (aCGH) analysis on DNA extracted from skin lesions of 13 patients affected from AECD8+L, 5 patients from ENK/T-NT and 21 patients from BPDCN.

In AECD8+ lymphoma, our results showed recurrent alterations of chromosomal regions found also in other CTCL, such as amplification of 3p21 (46% of patients), 7q (54%), 8q24 (54%), 16p (77%), 17q (92%), and the deletion of 9p21 (69%), and several alterations seemingly typical for AECD8+L: i.e. amplification of 11q12-q13 (69%), 22q (69%) and trisomy of 19 (69%). Within these amplified regions, the combination of duplication of JAK3 (chr. 19p13.11) and STAT3/ STAT5B (chr. 17q21) might explain the hyper-activation of JAK / STAT signaling pathway, with an increased proliferation and an increased anti apoptotic activity. Interestingly, constitutive Jak3 signaling in murine lymphopoiesis, in a bone marrow transplantation model, induces an aggressive lymphoproliferative disorder characterized by the expansion of $CD8^+$, $TCR\alpha\beta^+$ T cells. In addition chromosome 19 contains several genes that can lead to uncontrolled proliferation of cells if overexpressed, such as JUNB, JUND, KIR3DL2, AKT2, LYL1, BCL3 and RELB, alone or in combination with the proto-oncogene RELA, present in the amplified region 11q12-q13.

A retrospective case study of 5 white patients affected by ENK/T lymphoma (4 PC-ENK/T-NT and 1 ENK/T-N with cutaneous involvement) was also performed. Genomic alterations were detected by aCGH hybridization that showed gains of 1q, 7q and loss of 17p in the cases of PC-ENK/T-NT lymphomas and gain of 7q and loss of 9p, 12p, 12q in the case of ENK/T-N lymphoma. In our cases, the exclusively cutaneous presentation was not associated with a better prognosis. BPDCN is a rare, often fatal disease: all patients had skin lesions, 12 with extracutaneous disease at diagnosis. By aCGH there were chromosomal imbalances in all biopsies, with an average of 7 copy number alterations/case and losses more frequent than gains (141 vs 18); large interstitial/telomeric imbalances prevailing over the entire chromosome losses/gains (127 vs 32). Common deleted regions (CDR) were found on chromosomes 5, 7, 9, 12, 13 and 14. A CDR at 9p21.3, hosting CDKN2A suppressor gene (P16INK4a, p14ARF), was present in 15 cases; 6 in biallelic status. Chromosome 13 monosomy was found in 11 cases and we identified a minimal CDR on 13q13.1-q14.3, including RB1, CCNA1 and KPNAP3. In 12 cases a monoallelic CDR encompassed 12p13.2-p13.1, hosting CDKN1B (p27/KIP1). Additionally, 4 patients had del(7)(p12), a region harbouring IKZF/Ikaros, defective in cases of acute lymphoblastic leukaemia with poor prognosis. In conclusion, AECD8+L, PC_ENK/T-NT and BPDCN are aggressive neoplastic diseases showing complex genetic alterations, involving activation, proliferations and apoptosis, that may explain the poor response to therapy.

These data, complemented with gene expression analysis and immunohistochemical evaluation should help us in deciphering biologic and molecular mechanisms of these disease entities and may become important tools in diagnosis and classification or to find new therapeutic approaches.