Plasmablastic lymphoma: one or more tumours?

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In this issue of Haematologica, Ramis-Zaldivar et al. report on a series of plasmablastic lymphomas (PBLs), studied by a high-resolution approach to unravel the genomic landscape of the tumour, which has remained so far largely unexplored (1). According to the revised 4th edition of the WHO classification of tumours of haematopoietic and lymphoid tissues, plasmablastic lymphoma (PBL) is a rare and very aggressive disease entity with the diffuse proliferation of large neoplastic cells, most of which resemble B immunoblasts or plasmablasts that have a CD20-negative plasmacytic phenotype and more frequently carry MYC rearrangements (2). It was originally described in the oral cavity and frequently occurs in association with HIV infection, but it may also develop at other sites, predominantly extranodal, and in association with other causes of immunodeficiency (2). In the majority of cases, neoplastic cells turn to be EBV-infected (2). The differential diagnosis may include other varieties of diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), plasmablastic plasma cell myeloma (PPCM), and anaplastic large cell lymphoma. There is no standard of care at the time being and immunotherapy with anti-CD20 antibodies is unfeasible because of the lack of the target. DA-EPOCH has been recommended possibly in conjunction with cART in HIV-positive patients (3). However, studies of patients with PBL treated with chemotherapy regimens more intensive than CHOP did not identify a survival benefit and anyway the median overall survival with DA-EPOCH is disappointing, reported as 15±months in HIV-positive patients, and likely worse in HIV-negative patients (4). The usage of other therapies such as CART remains anecdotal (5), the optimal treatment of PBL being still an open issue.

Ramis-Zaldivar et al. applied to 34 PBLs a highly refined approach, which included mutational and copy number analyses, targeted gene expression profiling, fluorescence in situ hybridization, and immunohistochemistry (1). Such an array of techniques does represent the ideal way to explore the pathobiology of each neoplasm, if one aims to understand the possible range of mechanisms, which sustain it, and discover novel potential therapeutic targets.

The study highlights the molecular heterogeneity of PBL, which is in keeping with the scenario arising in the field of malignant lymphomas in general. For a long time, lymphomas have been intended as a monoclonal/monolithic condition. Nowadays, it becomes more and more evident that the same morphologic and phenotypic features can be sustained by a quite variable landscape of genetic aberrations with clones competing each other within the same neoplasm and under the influence of the microenvironment, thus leading to possible clonal selection, chemo-resistance and relapse (6).

Ramis-Zaldivar et al. show that PBL is characterized by high genetic complexity with very frequent MYC translocations (87%), gains of 1q21.1-q44, trisomy 7, 8q23.2-q24.21, 11p13-p11.2, 11q14.2-q25, 12p and
19p13.3-p13.13, losses of 1p33, 1p31.1-22.3, 13q and 17p13.3-p11.2, and recurrent mutations of STAT3, NRAS, TP53, MYC, EP300, CARD11, SOCS1, and TET2 (here listed in decreasing frequency) (1). Pathway enrichment analysis suggested a cooperative action between MYC alterations and MAPK and JAK-STAT signaling pathways. These alterations have been at least in part reported in previous studies (7,8). However, three major goals are achieved by Ramis-Zaldivar et al. First, the authors analyzed the clonal evolution in PBL and found that in 24 tumours the cancer cell fraction (CCF) included 250 copy number alterations and 107 mutations. The majority of these alterations revealed a wide spectrum of CCFs with the exception of TP53 mutations, 17 losses and 13q deletions, which turned out to be clonal. Notably, clonal and subclonal mutations affected the same protein domains, suggesting that the subclonal ones give similar advantage to the neoplastic cell. This is in keeping with what observed in liquid biopsy studies, which reveal that the mutational landscape of DLBCL is definitely wider in circulating tumoral DNA than in the diagnostic biopsy. (9) This finding underlines the potential occurrence of different clones at different anatomic sites (clonal heterogeneity) in lymphoid malignancies characterized by high genetic complexity, clones which can be selected by therapy and cause disease resistance or relapse (10). Second, the recorded constellation of genetic alterations can represent the rationale for targeted therapies (Figure 1), which are indeed urgently needed in the light of the poor response to conventional chemotherapies, including intensified regimens. The third important achievement of the study of Ramis-Zaldivar et al. consists in the demonstration of a clear-cut genetic difference between EBV-positive and EBV-negative PBLs. In particular, the latter showed higher genetic complexity and mutational load than the EBV-positive ones. EBV-negative cases were characterized by more frequent mutations affecting TP53, CARD11 and MYC as well as epigenome/chromatin modifiers, cell cycle and NF-kB pathway. Conversely, EBV-positive cases tended to carry frequent mutations involving genes of the JAK/STAT pathway. These findings are of interest for practical and conceptual reasons. They suggest different therapeutic targets depending on EBV-positivity or negativity. Furthermore, they strengthen the different pathobiology of virus infected lymphomas. By RNA sequencing, Abate et al. showed that 20 endemic BLs (eBL) from Uganda carried infection by Herpesviridae members other than EBV in 40% of cases, thus suggesting a polyviral condition, and revealed a mutations landscape different from sporadic BL (sBL) (with lower frequency of MYC, ID3, TCF3 and TP53 mutations, higher frequency of ARID1A mutations, and occurrence of not previously detected RHOA and CCNF mutations) (11). The latter findings suggested - as in the report of Ramis-Zaldivar et al. (1) - a dual mechanism of transformation in eBL and sBL, virus vs. mutation-driven respectively.

The ever-more application of a high-resolution approach to the analysis of malignant lymphomas is unraveling a scenario much more intriguing than thought only a few years ago. Within the body of a distinct entity as defined by the WHO Classification (2), tumours provided with different pathobiological characteristics are comprised, which offer different targets for ad hoc therapies. This has practical implications in the management of patients as well as in designing innovative therapeutic trials, if the final goal is to move to precision medicine.

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References


Legend to Figure 1: Array of potential targeted therapies based on the specific molecular abnormalities.
**Epigenetics**
- HDAC inhibitors
- Hypomethylating agents

**MAPK**
- BRAF inhibitors
- MEK 1/2 inhibitors
- ERK inhibitors

**JAK-STAT**
- JAK inhibitors
- STAT3 inhibitors
- Anti IL-6 mAb
- STAT3 antisense oligo
- STAT3 degrader

**TP53**
- DDR inhibitors
- Small molecule-mediated p53 reactivation

**MYC**
- BET inhibitors

**EBV**
- antiviral agents