Frequent Chromosome 1q Aberrations in HIV associated B-Cell Lymphoma Unclassifiable with Intermediate Features Between Diffuse Large B-Cell Lymphoma and Burkitt Lymphoma

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Human Immunodeficiency Virus (HIV) infection is known to be strongly associated with an increased risk of high grade B-Cell Lymphoma (such as Diffuse Large B-Cell Lymphoma and Burkitt Lymphoma). As South Africa has more than 5 million people living with HIV infection, this region sees a sharp increase in the diagnosis of high-grade lymphomas. HIV infection may associate with a number of atypical morphological features making it difficult to differentiate between classically described DLBCL and BL. As these two diseases have different prognosis and treatment, it is essential to accurately differentiate the type of disease and/or to diagnose the intermediate category of B-Cell Lymphoma, unclassifiable, with features intermediate between DLBCL and BL newly introduced in the 2008 WHO classification.

In this study, we report on twelve patients (seven males and five females) who presented with high grade B cell lymphoma and a cell morphology comprising a mixture of medium to large cells that expressed B Cell markers. Patients’ age ranged from 29 to 43 years old with a mean age of 34 years. Eight patients had a documented HIV positive status. Complex cytogenetic features associated with atypical morphologic features best fitted the diagnosis of B cell lymphoma unclassifiable, with features intermediate between DLBCL and BL.

Conventional cytogenetics analysis revealed the presence of a complex karyotype in all cases. The chromosomes number varied from 46 to 49 with the exception of one case that had near-tetraploid cells (69 to 84 chromosomes). Ten cases had a t(8;14) classical Burkitt translocation involving the Immunoglobulin heavy chain gene as a partner, and one case had a variant Burkitt translocation t(8;22) involving the lambda light chain gene. Double hits were seen in two cases. In both cases, a translocation t(3;22)(q27;q11) rearranged the BCL6 gene in addition to a t(8;14). MYC and BCL6 genes rearrangements were confirmed using fluorescence in situ hybridization with the MYC and BCL6 break-apart probes (Abbott Molecular) and with the IGH/MYC/CEP probes. The most common secondary chromosomal aberration associated with a MYC rearrangement, was a chromosome 1 long arm structural abnormality present in nine cases, (75%) and resulting in a full trisomy 1q (n=3 ), or in partial duplication/ triplication of chromosome 1q (n=3), with both types of aberrations associated in 3 cases.

Genome-Wide Affymetrix SNP6.0 array analysis was used to delineate chromosome 1q regions of gains. In brief, high molecular weight tumor DNA was extracted from tumor cells together with normal controls. DNA was processed and hybridized to the arrays according to
the manufacturer's instructions. Data analysis was performed using the dChip software and Circulary Binary Segmentation.

Copy number analysis using SNP arrays delineated three minimum regions of gains on the chromosome 1 long arm, 1q21.1q23.3, 1q24.1q24.2 and 1q32.1q32.2. The smallest region of amplification 1q24.11q24.2 included 27 genes of which the RCSD1 gene normally expressed in B-cells and previously found to be involved in acute B cell lymphoid leukemia (De Braekeleer et al 2007). These regions were smaller than 1q gains previously mapped by array comparative genomic hybridization in acute lymphoblastic leukemia and BL (Davidsson, et al 2007). Abnormalities of chromosome 7q were also non-randomly detected in four cases, in the form of trisomy 7q, or partial 7q duplication. Gains of 1q and 7q are known to occur in 20% and 10% of Burkitt lymphomas respectively (Boerma et al 2009; Scholtysik et al 2010). On the basis of these molecular cytogenetic features, we argue that these aggressive immunodeficiency associated, mostly t(8;14) positive lymphomas, represent advanced, clonally evolved forms of BL. These findings support the notion that there are distinguishable subgroups in DLBCL/BL intermediate lymphomas.

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