THE MOLECULAR PROFILE OF ORAL PLASMABLASTIC LYMPHOMAS IN A SOUTH AFRICAN POPULATION SAMPLE

by

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Submitted in fulfillment of the requirements for the degree PhD in the Faculty of Health Sciences, University of Pretoria

Date submitted: April 2011
DECLARATION

I, Sonja Catharina Boy, hereby declare that the work on which this thesis is
based, is original and that neither the whole work nor any part of it has been, is
being, or shall be submitted for another degree at this or any other university,
institution for tertiary education or examining body.

____________________

SC Boy
I DEDICATE THIS THESIS TO:

MY TWO CHILDREN, MARINUS AND NATANYA, BOTH BORN DURING THE FOUR YEAR DURATION OF THIS PROJECT, AND WHO HAD TO SHARE MY TIME AND LOVE WITH THE BIGGEST RESEARCH PROJECT OF MY LIFE

MY PARENTS, JOSEPH AND DINA FOR THEIR UNCONDITIONAL LOVE AND SUPPORT TO FULFILL THIS DREAM

MY HEAVENLY FATHER WHO GAVE ME THE IMPOSSIBLE STRENGTH TO PERSIST
SUMMARY

Plasmablastic lymphoma (PBL) was originally described in 1997 as an AIDS-associated tumour although cases have been described in individuals not infected with HIV. Due to the high number of people living with HIV in South Africa, a substantial number of cases are diagnosed annually and 45 cases were included in this study. This represented the largest cohort of PBL affecting the oral mucosa published to date. Three main aspects of PBL were investigated: pathological features, viral status and certain genetic characteristics.

The results from the genetic studies were the most important and interesting. These included rearrangements of the \textit{IGH} gene in 63% and \textit{MYC}-rearrangements in 62% of PBL’s. Seven of 43 cases (16%) showed rearrangement of both the \textit{IGH} gene alleles, a finding never described before. New genetic findings also included increased \textit{CCND1} gene copy numbers in 17/41 (42%) and increased \textit{IGH} gene copy numbers in 6/41 (15%) of cases.

The exact role of \textit{MYC}-rearrangements in the development of PBL is unclear. Many factors may be responsible for \textit{MYC} deregulation but in the case of PBL of the oral cavity the possible role of Epstein Barr Virus (EBV) infection was considered. All but one of the patients with known HIV-status (32/45) was HIV positive and I supported the proposal that the diagnosis of PBL should serve as a sign of immunodeficiency, either as diagnostic thereof or as a predictor of a progressive state of immunodeficiency in patients with known HIV/AIDS status. The HIV-negative patient in this study was the only one that presented with an EBV-negative PBL on \textit{in situ} hybridisation. The clinico-pathological features of the current study therefore strongly suggested an association between EBV, PBL and HIV/AIDS although the exact nature thereof remains uncertain.

Routine genetic evaluation of tumours diagnosed as PBL should be introduced, as this may have prognostic and eventually treatment implications in the future. The exact panel of genes to be evaluated with a possible diagnosis of PBL
should still be determined but examination of *IGH* and *MYC* for rearrangements should be included.

This study proved the histomorphological features including the degree of plasmacytic differentiation not to have any diagnostic role although its prognostic value should be determined. The results of the immunohistochemical investigations performed in this study confirmed PBL always to be negative for CD20 but proved PBL not to be a morphological or immunohistochemical diagnosis by any means.

In conclusion, it became clear that PBL should never be diagnosed without thorough clinical, systemic, pathological and genetic investigations, especially in the backdrop of HIV/AIDS. No pathologist should make the diagnosis of PBL and no clinician should accept such a diagnosis or decide on the treatment modality for the patient involved unless all other possibilities of systemic plasma cell disease have been excluded.

**Key Words:**

Lymphoma; HIV/AIDS; plasmablastic lymphoma; Epstein Barr virus (EBV); *MYC* rearrangement;
PUBLICATIONS AND PRESENTATIONS

Publications

- Boy SC, van Heerden MB, Babb C, van Heerden WFP, Willem P. *MYC* aberrations and EBV infection are major role players in the pathogenesis of HIV-related Plasmablastic lymphomas. Accepted for publication in the *Journal of Oral Oncology*, January 2011.

National Congress presentations:


International Congress presentations

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Dr. C Babb. Co-worker and Medical Scientist, Department of Haematology and Molecular Medicine, the National Health Laboratory Services (NHLS).

Mrs MB Van Heerden. Co-worker, friend and Head Medical Technician of the Department of Oral Pathology and Oral Biology, School of Dentistry, Faculty of Health Sciences, University of Pretoria.

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The micrograph taken from a case of PBL confirms all tumour cells to be CD20 negative although reactive B-cells served as positive internal control.

The micrograph was taken from a case of PBL and confirms all the tumour cells to be CD3 negative. Reactive T-cells served as a positive internal control for the CD3 stain.

The micrograph was taken from a case of PBL again confirming the tumour cells to be CD3 negative. More abundant reactive T-cells staining positive with CD3 is however present.

The micrograph represents a PBL case with typical diffuse and strong, red-brown positive nuclear staining for the proliferation marker, Ki-67.

A micrograph of case 17 showing only focal positivity for Ki-67.

Strong and diffuse positive cytoplasmic staining with MUM in the tumour cells of a case of PBL.

The micrograph was taken of the MUM stain of case 43. Only focal positivity was present.

Strong positive staining for CD45 is present on the cell membranes of most of the tumour cells in this PBL. Some reactive B- and T-cells are also seen on this micrograph.

Red-brown granular staining for CD79a is seen in the cytoplasm of the tumour cells in this case of PBL.

The micrograph represents a case of PBL where positive
staining for CD79a is seen in only the reactive B-cells but not in the tumour cells.

18 The micrograph shows diffuse positive CD38 staining on the cell membranes of the tumour cells of this case of PBL. Membranous staining clearly delineates the cell membranes of some of the tumour cells.

19 Positive staining for CD38 is seen as red-brown granular staining in the reactive plasma cells. None of the larger tumour cells stained positive for CD38 in this case of PBL.

20 Diffuse positive staining for CD138 is present on the cell membranes of most of the tumour cells in this case of PBL. The membranous stain delineates the cytoplasmic rim of the tumour cells.

21 Positive staining for CD138 is seen only in reactive plasma cells of this PBL case. None of the tumour cells stained with this marker.

22 The micrograph shows a case of PBL that was negative for CD138. Strong positive staining for CD138 is however visible in the basal epithelial cells of the overlying covering epithelium of the oral mucosa.

23 The micrograph was taken from a case of diffuse large B-cell lymphoma that served as positive control for the ALK protein stain. Red-brown granular staining is seen in the cytoplasm of the tumour cells.

24 This case of PBL shows clear kappa light chain restriction with
diffuse red-brown granular cytoplasmic staining for the kappa light chain (a) but with no staining for the lambda light chain (b) in the tumour cells. Reactive plasma cells served as positive internal control in all negative light chain stains.

25 The micrograph shows positive, black nuclear staining for HHV-8 on the Kaposi sarcoma section hybridised with the HHV-8 probe. This served as positive control for the HHV-8 ISH.

26 Positive, black nuclear staining for EBV can be seen in many of the tumour cell nuclei on the micrograph of this case of PBL.

27 This is a close-up view to demonstrate the black nuclear staining accepted as positive for EBV ISH.

28 This micrograph was taken from the brain section that served as negative control for the EBV ISH. No nuclear staining is visible.

29 DAPI stained interphase nuclei of a PBL case hybridised with the LSI IgH dual colour BA rearrangement probe (Vysis®, Abbot Laboratories) showing no BA. Two yellow fusion signals are seen per cell nucleus. Spectrum orange represents the 3’ probe and spectrum green represents the 5’ probe, which covers almost the entire variable region of the IGH gene.

30 DAPI stained interphase nuclei of a PBL case hybridised with the LSI IgH dual colour BA rearrangement probe (Vysis®, Abbot Laboratories). Two yellow fusion signals are present in most cell nuclei and no break apart was present in this case. The arrow demonstrates an area of overlapping cell nuclei which created the impression of three fusion signals in one cell. FISH analysis was therefore always performed in single cell nuclei only.
31 DAPI stained interphase nuclei of a PBL case hybridised with the LSI \textit{IGH} dual colour BA rearrangement probe (Vysis®, Abbot Laboratories). \textit{IGH} rearrangement of one allele is present in some cell nuclei represented as one orange (3’) and one green (5’) signal apart from each other. The unaffected allele on chromosome 14 is seen as one yellow fusion signal.

32 DAPI stained interphase nuclei of a case of PBL hybridised with the LSI \textit{IGH} dual colour BA rearrangement probe (Vysis®, Abbot Laboratories) showing IgH rearrangement of chromosomes 14. Two to three copies of orange (3’) and one to four copies of green (5’) signals are seen in the tumour cell nuclei and there are no normal fusion signals. There are no fusion signals; all \textit{IHG} copies have a gene rearrangement.

33 DAPI stained interphase nuclei of a case of PBL hybridised with the LSI \textit{IGH} dual colour BA rearrangement probe (Vysis®, Abbot Laboratories) showing IgH rearrangement affecting both alleles on chromosome 14. More than three orange (3’) and one to three green (5’) signals are seen in the tumour cell nuclei signalling additional copies of IGH. No normal fusion signals are visible in any nucleus.

34 DAPI stained interphase nuclei of case 6 hybridised with the \textit{MYC/IGH} dual colour dual fusion translocation probe (Vysis®, Abbot Laboratories). The nuclear signals represent a normal pattern with two spectrum aqua (chromosome 8 CEP), two spectrum orange (\textit{MYC}-gene), and two spectrum green (\textit{IGH}-gene) signals per cell nucleus (arrows). No yellow fusion signals indicative of a t(8;14) are visible here.

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35 DAPI stained interphase nuclei of case 2 hybridised with the *MYC/IGH* dual colour dual fusion translocation probe (Vysis®, Abbot Laboratories). Positive t(8:14) translocation is demonstrated by the positive yellow fusion signals. The presence of one fusion signal in many cells likely reflects the loss of one translocation derivative. Orange signals represent the *MYC* gene on chromosome 8 and the green signals represent the *IGH* gene on chromosome 14.

36 DAPI stained interphase nuclei of case 11 hybridised with the LSI *MYC* dual colour BA rearrangement probe (Vysis®, Abbot Laboratories) showing MYC rearrangement of one allele as one spectrum orange (5') and one spectrum green (3') signal apart from each other. The normal yellow fusion signal represents the unaffected allele on chromosome 8.

37 DAPI stained interphase nuclei of complex case 27 hybridised with the *IGH/CCND1* dual colour dual fusion translocation probe (Vysis®, Abbot Laboratories). Positive t(11;14) translocation is demonstrated by the positive yellow fusion signals. Two fusion signals are visible in some cells. Orange signals represent the *CCND1* gene on chromosome 11 and the green signals represent the *IGH* gene on chromosome 14. The *IGH* gene was also shown to be rearranged on the *IGH* BA analysis.

38 DAPI stained interphase nuclei of case 7 hybridised with the *IGH/CCND1* dual colour dual fusion translocation probe (Vysis®, Abbot Laboratories). Three to six copies of the *CCND1* gene on chromosome 11 are represented by the spectrum orange signals. A cell with seven green signals, representative of three to four *IGH* signals on chromosome 14 is also shown here. *IGH* was also rearranged on the *IGH* BA probe analysis of this case.
DAPI stained interphase nuclei of case 38 hybridised with the
*IGH/CCND1* dual colour dual fusion translocation probe (Vysis®,
Abbot Laboratories). Four to ten copies of the *CCND1* gene on
chromosome 11 are represented by the orange signals. Green
signals represent the *IGH* gene on chromosome 14 which also
shows an increased copy number with up to 10 copies per
nucleus. The *IGH* gene was also rearranged on the *IGH BA*
probe analysis of this case.

DAPI stained interphase nuclei of case 4 hybridised with the
*MYC/IGH* dual colour dual fusion translocation probe (Vysis®,
Abbot Laboratories). The nuclear signals have a complex
pattern with various copy numbers of the *IGH*-gene
(represented by spectrum green) and two to four yellow fusion
signals signaling a *MYC-IGH* translocation. Three CEP 8 signals
(represented by spectrum aqua), is seen in some cell nuclei.

DAPI stained interphase nuclei of case 38 hybridised with the
*LSI BCL6* dual colour BA rearrangement probe (Vysis®, Abbot
Laboratories) showing no rearrangement of the *BCL6* gene but
with gains of the BCL6 locus represented by three fusion signals
in a significant number of the cell nuclei. Spectrum orange
represents the 5’ *BCL6* probe and spectrum green represent the
3’ probe.

The micrograph shows an example of a false positive HHV-8 in
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<table>
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<th>Acquired immune deficiency syndrome</th>
<th>AIDS</th>
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<tr>
<td>Activation-induced cytidine deaminase</td>
<td>AID</td>
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<tr>
<td>Anaplastic lymphoma kinase-1</td>
<td>ALK-1</td>
</tr>
<tr>
<td>Alkaline phosphatase substrate buffer</td>
<td>AFSB</td>
</tr>
<tr>
<td>B-cell lymphoma-6 protein</td>
<td>BCL6</td>
</tr>
<tr>
<td>B-lymphocyte induced maturation protein</td>
<td>BLIMP-1</td>
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<tr>
<td>Break apart</td>
<td>BA</td>
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<tr>
<td>5-bromo-4-chloro-3-indolylphosphate</td>
<td>BCIP</td>
</tr>
<tr>
<td>Burkitt’s lymphoma</td>
<td>BL</td>
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<td>Centromere enumeration probe</td>
<td>CEP</td>
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<tr>
<td>Class-switch recombination</td>
<td>CSR</td>
</tr>
<tr>
<td>Cluster of differentiation</td>
<td>CD</td>
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<td>Constant regions</td>
<td>C regions</td>
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<tr>
<td>Cyclin D1</td>
<td>CCND1</td>
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<tr>
<td>4’, 6-Diamidino-2-phenylindole dihydrochloride</td>
<td>DAPI</td>
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<td>Diffuse large B-cell lymphoma</td>
<td>DLBCL</td>
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<tr>
<td>Diversity gene segments</td>
<td>D segment</td>
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<tr>
<td>Deoxyribonucleic acid</td>
<td>DNA</td>
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<tr>
<td>Epithelial membrane antigen</td>
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<tr>
<td>Epstein Barr virus</td>
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<td>EBV-encoded latent membrane protein-1</td>
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<tr>
<td>EBV-encoded RNA</td>
<td>EBER</td>
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<td>Ethylene diamine tetra-acetic acid disodium salt</td>
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<td>Extra-medullary plasmacytomas</td>
<td>EMPC</td>
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<tr>
<td>Fibroblast growth factor receptor</td>
<td>FGFR</td>
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<tr>
<td>Fluorescein isothiocyanate</td>
<td>FITC</td>
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<tr>
<td>Term</td>
<td>Abbreviation</td>
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<tr>
<td>-----------------------------------------------------------</td>
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<tr>
<td>Fluorescent <em>in situ</em> hybridisation</td>
<td>FISH</td>
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<tr>
<td>Formalin fixed paraffin embedded</td>
<td>FFPE</td>
</tr>
<tr>
<td>Germinal center</td>
<td>GC</td>
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<td>Haematoxylin and eosin</td>
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<td>Heat induced epitope retrieval</td>
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<td>Highly active antiretroviral therapy</td>
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<td>Human herpesvirus-8</td>
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<td><em>In situ</em> hybridisation</td>
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</tr>
<tr>
<td>Lambda light chain</td>
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<tr>
<td>Major histocompatibility complex</td>
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<td>Monoclonal gammopathy of undetermined significance</td>
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<td>Mucosa associated lymphoid tissue</td>
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<td>Nitroblue tetrazolium</td>
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<td>--------------</td>
</tr>
<tr>
<td>Phosphate buffered saline buffer</td>
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<tr>
<td>Polymerase chain reaction</td>
<td>PCR</td>
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<tr>
<td>Primary effusion lymphoma</td>
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<tr>
<td>Recombination activating enzyme 1/2</td>
<td>RAG1/2</td>
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<tr>
<td>Revised European American Classification of Lymphoid Neoplasms</td>
<td>REAL</td>
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<tr>
<td>Saline sodium citrate</td>
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<td>Sodium thiocyanate</td>
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<td>Somatic hypermutation</td>
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<td>Tris Buffered Saline</td>
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Ethics Clearance Certificate from the Research Ethics Committee of the Faculty of Health Sciences, University of Pretoria