

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

**by**

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## 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.

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**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 *IGH* gene in 63% and *MYC*-rearrangements in 62% of PBL's. Seven of 43 cases (16%) showed rearrangement of both the *IGH* gene alleles, a finding never described before. New genetic findings also included increased *CCND1* gene copy numbers in 17/41 (42%) and increased *IGH* gene copy numbers in 6/41 (15%) of cases.

The exact role of *MYC*-rearrangements in the development of PBL is unclear. Many factors may be responsible for *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 *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, Raubenheimer E, van Heerden WFP. Plasmablastic lymphomas with light chain restriction – Plasmablastic extramedullary plasmacytomas? *Journal of Oral Pathology and Medicine*, 39 (5): 435-439, 2010.
- 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:

- Van Heerden M, Boy SC, van Heerden WFP. Necessity of a negative control as well as the stringency of the post hybridization wash in the *in situ* hybridization protocol. *Pathvine IAP South African Division Congress*. Cape Town, South Africa, September 2010.

### International Congress presentations

- Boy SC, van Heerden MB, Babb C, van Heerden WFP. The immunohistochemical and viral profile of plasmablastic lymphomas in a South African population sample. *22<sup>nd</sup> European Congress of Pathology*, Florence, 2009.
- Boy SC, van Heerden MB, Babb C, van Heerden WFP, Willem P. Burkitt's translocation is a common finding in plasmablastic lymphomas. *15<sup>th</sup> International congress of IAOP*, Seoul, Korea, August 2010.

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## LIST OF ABBREVIATIONS

Acquired immune deficiency syndrome	AIDS
Activation-induced cytidine deaminase	AID
Anaplastic lymphoma kinase-1	ALK-1
Alkaline phosphatase substrate buffer	AFSB
B-cell lymphoma-6 protein	BCL6
B-lymphocyte induced maturation protein	BLIMP-1
Break apart	BA
5-bromo-4-chloro-3-indolylphosphate	BCIP
Burkitt's lymphoma	BL
Centromere enumeration probe	CEP
Class-switch recombination	CSR
Cluster of differentiation	CD
Constant regions	C regions
Cyclin D1	CCND1
4', 6-Diamidino-2-phenylindole dihydrochloride	DAPI
Diffuse large B-cell lymphoma	DLBCL
Diversity gene segments	D segment
Deoxyribonucleic acid	DNA
Epithelial membrane antigen	EMA
Epstein Barr virus	EBV
EBV-encoded latent membrane protein-1	LMP-1
EBV-encoded RNA	EBER
Ethylene diamine tetra-acetic acid disodium salt	EDTA
Extra-medullary plasmacytomas	EMPC
Fibroblast growth factor receptor	FGFR
Fluorescein isothiocyanate	FITC

Fluorescent <i>in situ</i> hybridisation	FISH
Formalin fixed paraffin embedded	FFPE
Germinal center	GC
Haematoxylin and eosin	H&E
Heat induced epitope retrieval	HIER
Highly active antiretroviral therapy	HAART
Human herpesvirus-8	HHV-8
Human immunodeficiency virus-1	HIV-1
Hydrochloric acid	HCl
<i>In situ</i> hybridisation	ISH
Interferon regulatory factor 4	<i>IRF-4</i>
Interleukin 6	IL-6
Immunoglobulins	Ig
Immunoglobulin heavy chain gene	<i>IGH</i>
Junctional gene segments	J segment
Kappa light chain	κ
Lambda light chain	λ
Major histocompatibility complex	MHC
Monoclonal gammopathy of undetermined significance	MGUS
Mucosa associated lymphoid tissue	MALT
Multiple myeloma	MM
Multiple Myeloma oncogene-1	MUM-1
Nitroblue tetrazolium	NBT
Non-Hodgkin's lymphoma	NHL
Not otherwise specified	NOS



Phosphate buffered saline buffer	PBS
Plasmablastic lymphoma	PBL
Polymerase chain reaction	PCR
Primary effusion lymphoma	PEL
Recombination activating enzyme 1/2	RAG1/2
Revised European American Classification of Lymphoid Neoplasms	REAL
Saline sodium citrate	SSC
Sodium thiocyanate	NaSCN
Somatic hypermutation	SHM
Tris Buffered Saline	TBS
Variable regions	V regions
World Health Organisation	WHO
X-box binding protein-1	<i>XBP-1</i>

## **LIST OF ANNEXURES**

Ethics Clearance Certificate from the Research Ethics Committee of the Faculty of Health Sciences, University of Pretoria