HIV AND LYMPHADENOPATHY

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DECLARATION

I, Sagren Naidoo declare that this thesis is my own work. It is being submitted for the degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University

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Dedicated to my family

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Abstract

Lymphadenopathy is common in HIV-infected individuals as lymphoid tissue is a major target and reservoir of the Human immunodeficiency virus (HIV). Lymphadenopathy may occur at any stage of HIV infection. Lymphadenopathy is also a common clinical problem confronting the primary care physician. When lymphadenopathy occurs in the setting of underlying immunodeficiency, both benign and malignant aetiologies need to be considered. Indeed, in our study of 43 patients with HIV seropositivity, where a lymph node biopsy was performed (i.e. in 40 patients), TB was the most common cause of significant lymphadenopathy (16/40 - 60%), followed by malignancy (10/40 - 25%). However, 9/40 patients (22.5%) in this group, also had reactive lymphadenopathy, which may or may not be related to the HIV.

The primary objectives of this study were: i) to define the causes and the clinical patterns of presentation of lymphadenopathy in an HIV sero-positive population. Secondary objectives were: i) To review the appropriateness of the investigations that may suggest or exclude a possible cause of the lymphadenopathy and ii) To correlate the results of a FNA and/or lymph node biopsy when this was performed. Furthermore, iii) it was questioned whether it was possible to identify criteria indicating a need for a FNA and/or a lymph node biopsy.

A total of 43 Black African adult patients, 21 males (49%) and 22 females (51%), were prospectively studied during 2004 and 2005. The median age was 33 years (range 16-52 years). The median duration of lymphadenopathy was 16weeks (3-52 weeks).

A history of constitutional symptoms was most common among the patients diagnosed with TB, but did not reach statistical significance. In our study, the finding of lymphadenopathy in the cervical and axillary regions did not differentiate between malignancy, TB and reactive nodes. However, the presence of these nodes was suggestive of significant pathology i.e.

malignancy or TB. The presence of hard nodes was more in keeping with a diagnosis of malignancy and/or TB. The presence of matted nodes was classical of TB.

In the ten patients diagnosed with malignancy, three had significant peripheral lymphadenopathy at only a single site, emphasizing the point that malignancy may present with localised adenopathy as well as generalised adenopathy. The lymph node biopsy in the three patients with localised adenopathy showed non-Hodgkin's lymphoma.

Lymphadenopathy in HIV positive patients does not seem to follow any specific clinical pattern. The nodes, in addition to the presence of malignancy, TB or other pathology may be distorted by the presence of PGL. This concept may still be true if one considers that some of the patients did indeed have more than one pathology in their lymph nodes. One patient was diagnosed as having a metastatic neuroendocrine tumour on the first FNA and TB on a second FNA. Lymph node biopsy was consistent with a neuroendocrine tumour. However, the patient also tested positive for acid fast bacilli on a sputum sample. Similarly, another patient had KS on one lymph node and reactive changes on another node from the same biopsy site. A third patient had TB and reactive lymphadenopathy from the same biopsy site.

Even though there was no correlation between chest radiographs and lymph node biopsy pathology in our study, the finding of intra-thoracic lymphadenopathy suggested more significant pathology, such as TB or malignancy.

A patient with unexplained cytopenias, especially with a pancytopenia should ideally have a bone marrow aspirate and trephine biopsy to clearly elucidate the underlying pathology. Interestingly in our study, a patient diagnosed with reactive lymphadenopathy on FNA and subsequently shown to have Castleman's disease on lymph node biopsy, had a granuloma on bone marrow trephine consistent with TB.

A relative monocytosis was suggestive of malignancy in our study, but may also be an indication of viral latency, as most of these patients with monocytosis also had a CD4+ lymphocyte count above 200 cells/mm^3.

In our study, thirty patients had both a FNA and a lymph node biopsy for comparison. Comparing FNA with lymph node biopsy as the true positive, eleven patients were diagnosed with TB, four with malignancy, three as reactive and two as having other aetiologies of their lymphadenopathy.

In the discrepant group of ten patients comparing FNA to Biopsy, five patients were diagnosed as having reactive lymph nodes on FNA, but the biopsy confirmed two with Castleman's disease, two with NHL and one with TB. One patient diagnosed as TB on FNA, had KS on biopsy. Another patient with a lymphoepithelial cyst on FNA had reactive lymphadenopathy on biopsy. A further patient diagnosed with TB on FNA had a sub-optimal lymph node biopsy.

The differences in FNA and biopsy results could be explained as 'errors' of sampling. In other words the FNA and biopsy were done at different sites in the same patient, and therefore these patients potentially had more than one pathological cause for their lymphadenopathy. Also, less tissue was available for review from the FNA specimen and immunohistochemical stains were not possible on the paucity of FNA material available.

In the patients who had a lymph node biopsy, sixteen had TB, ten were diagnosed with malignancy (seven with NHL, two with KS and one with a neuroendocrine tumour). The other group included two patients with Castleman's disease, one with a lymphoepithelial cyst, one with fibrous tissue and one as having a suboptimal biopsy. One patient had a biopsy which showed KS on one lymph node and a second node as having reactive features. A second patient had a diagnosis of TB and reactive lymphadenopathy on the same biopsy. Nine patients had reactive lymphadenopathy on biopsy. Using chi-square analysis, the

specificity and sensitivity of FNA was compared to the lymph node biopsy results. In general, the low specificity and sensitivity in the different groups with the wide confidence intervals may be due to the small sample size in our patient population. Nevertheless, when comparing FNA to lymph node biopsy for the diagnosis of malignancy, the specificity and sensitivity was 100% and 43% respectively, with wide confidence intervals. This indicates that although a positive result for malignancy on FNA is highly specific, FNA for the diagnosis of malignancy is much less sensitive and a significant number of patients could be missed if the diagnosis is based on the FNA only. The specificity and sensitivity for the diagnosis of TB was 86% and 95% respectively (FNA is less specific for TB, but more sensitive). Reactive lymphadenopathy had a lower specificity and sensitivity of 80% and 60% respectively. Similarly, the specificity and sensitivity for the diagnosis of other pathologies was 86% and 40% respectively. These results underline the importance of performing a lymph node biopsy (which remains the 'gold standard'), more particularly where malignancy is suspected or where a reactive FNA result may not be sensitive enough to exclude a more definitive diagnosis for the lymphadenopathy.

The clinical haematology department receives referrals of lymphoma patients from other hospitals and other departments within the hospital (such as surgery, ENT etc). Many of these patients are referred with a biopsy proven lymphoma. Morever, 60-70% of all patients with lymphoma(both NHL and HD) are HIV sero-positive. As a result of this pattern of referral, the reflection of the cause of lymphadenopathy at this hospital may not have been obtained in this study. This should be regarded as a limitation of the study. Other shortcomings of this study include the small sample size, making comparisons from a statistical point of view difficult to interpret.

Nevertheless, the study emphasizes the importance of investigating the cause of significant lymphadenopathy in HIV seropositive individuals, as in 65% of such individuals a

pathological cause such as TB or malignancy is found. The high discordance rates of 33,3% between the FNA and the lymph node biopsy, underlines the fact that a lymph node biopsy should remain the investigation of choice, where a definitive diagnosis needs to be established, particularly with respect to malignancy.

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List of Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
bDNA	Branched DNA
CDC	Centres for Disease Control and Prevention
CMV	Cytomegalovirus
CNS	Central Nervous System
ELISA	Enzyme linked-immunosorbent assay
Env	Envelop
EPP	Estimation and Projection Package
Gag	Glycosoaminoglycan
Gp120	Glycoprotein 120
Gp41	Glycoprotein 41
HD	Hodgkin's disease
HSV	Herpes Simplex Virus
HTLV-III	Human T-lymphotropic Virus type III
LAV	Lymhadenopathy Associated Virus
NHL	Non-Hodgkin's Lymphoma
PGL	Persistent Generalized Lymphadenopathy
Pol	Polymerase
Pr	Probability
RIPA	Radioimmunoprecipitation assay
PCR	Polymerase chain reaction
RT	Reverse Transcriptase
RT-PCR	Reverse Transcriptase PCR
TBL	Tuberculous Lymphadenitis
NASBA	Nucleic acid sequence-based amplification
UNAIDS	Joint United Nations Program on HIV/AIDS
VSV	Varicella Zoster Virus