

Diagnostic accuracy of fine needle aspiration cytology in providing a diagnosis of cervical lymphadenopathy among HIV-infected patients

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Abstract

Background: Opportunistic infections and malignancies cause lymphadenopathy in HIV-infected patients. The use and accuracy of fine needle aspiration cytology in diagnosing of cervical lymphadenopathy among HIV-infected patients is not well studied in Uganda.

Objective: The aim of this study was to determine the diagnostic accuracy of fine needle aspiration cytology in providing a diagnosis of cervical lymphadenopathy among HIV-infected patients in Uganda.

Methods: We consecutively recruited adult HIV-infected patients with cervical lymphadenopathy admitted to Mulago Hospital medical wards. Clinical examination, fine needle aspiration and lymph node biopsy were performed. We estimated the sensitivity, specificity; negative and positive predictive values using histology as the gold standard.

Results: We enrolled 108 patients with a mean age of 33 years (range, 18-60), 59% were men and mean CD4 was 83 (range, 22-375) cells/mm³. The major causes of cervical lymphadenopathy were: tuberculosis (69.4%), Kaposi's sarcoma-KS (10.2%) and reactive adenitis (7.4%). Overall fine needle aspiration cytology accurately predicted the histological findings in 65 out of 73 cases (89%) and missed 7 cases (9.5%). With a sensitivity of 93.1%, specificity of 100%, positive predictive value of 100% and negative predictive value of 78.7% for tuberculosis and 80%; 98.4%;88.9% and 98.9% for KS respectively. No fine needle aspiration complications were noted.

Conclusions: Fine needle aspiration cytology is safe and accurate in the diagnosis of tuberculosis and KS cervical lymphadenopathy among HIV-positive patients.

Keywords: Fine needle aspiration cytology, cervical lymphadenopathy, HIV

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Introduction

Significant asymmetrical lymphadenopathy is a common problem in HIV infected adults. In developing countries with a high incidence of tuberculosis, tuberculous lymphadenitis (TBLN) is one of the most frequent causes of lymphadenopathy and occurs with increased frequency in HIV positive individuals.¹⁻³ Several other opportunistic infections can present similar-

ly including; Cryptococcus infection, toxoplasmosis and pyogenic infections. In HIV/AIDS patients, there is also an increased risk of development of malignancies such as Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL) which may present similarly^{4,5}.

In the past decade, fine needle aspirate cytology (FNAC) has assumed an important role in the diagnosis of peripheral lymphadenopathy as an alternative procedure which is less invasive, faster and cheaper than excision biopsy.⁶⁻⁸ Unfortunately, FNAC has not been widely utilized in Uganda, as most clinicians still use surgical excision biopsies. Such biopsies are fairly invasive; need more resources, and a longer time to diagnosis. Diagnostic accuracy of FNAC with its pitfalls has been extensively reviewed by Schmidt.⁹ He argues that a set standard should be followed and in the design and reporting of these studies to avoid bias. FNAC has gen-

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erally been found to be accurate in diagnosing different aetiologies in HIV-infected patients but most of these studies have been retrospective.^{9,10}

The diagnostic accuracy of FNAC among HIV-infected patients with cervical lymphadenopathy in Uganda is largely unknown; neither do we know the leading causes of lymphadenopathy in this patient population. There is therefore need to ascertain the accuracy and causes of cervical lymphadenopathy and to evaluate simpler, less invasive methods for making a diagnosis. We hypothesized that FNAC is as good as histology in the diagnosis of lymphadenopathy among HIV-positive patients. We determined the diagnostic accuracy of FNAC in the evaluation of cervical lymphadenopathy in adult HIV-infected patients and established the common causes in Mulago national referral hospital.

Methods

Participants

This was a cross-sectional study of diagnostic accuracy in which we consecutively recruited adult HIV-infected patients with cervical lymphadenopathy who were admitted to Mulago national referral hospital medical wards in Kampala, Uganda, between February 2007 and June 2007. Mulago national referral hospital is one of two national referral hospitals. It is located in the center of the capital city of the country called Kampala. The hospital admits most of the HIV-infected patients from the surrounding specialist centers as well as other hospitals throughout the country. HIV testing is routinely provided to all the patients that are admitted through the emergency unit on an 'opt out' basis.

We included patients who were 18 years or older and had documented HIV-1 infection with cervical lymphadenopathy (considered as the largest lymph node diameter > 1 centimeter). Patients with a prior histopathologic diagnosis of their cervical lymphadenopathy were excluded from the study.

We interviewed participants using a structured questionnaire to obtain information on the socio-demographic characteristics, history of prior treatment for TB or any other opportunistic infection as well as the presence of fever, cough for more than two weeks, night sweats and loss of weight.

Study physicians examined participants to assess the location, number and consistency of enlarged cervical

lymph nodes, as well as height, weight, Karnosky score, and WHO HIV stage. Blood was drawn for CD4 T cell count testing.

Test methods

Histology of the lymph node aspirate was used as the gold standard for all the aetiological diagnoses. We performed fine needle aspiration on the cervical lymph node of each participant. Under sterile conditions, we used a 23-gauge needle and 10 ml syringe for aspiration of the largest node, allowing 3-5 passes through the node. The aspirate was flushed onto a slide and spread to make a thin smear, taking precautions to avoid contamination especially to the eyes.

Next local anesthetic was infiltrated in the skin above a selected non-fluctuant lymph node that was easily accessible for biopsy. Under sterile conditions, the node was biopsied and put in a container with 10% formalin for histological processing and examination. Any discomfort or side effects were monitored over the next four hours. The time taken to perform the FNA, biopsy and cytology were recorded.

The aspirated material was spread on five glass slides. One slide was fixed immediately with 95% ethyl alcohol, and the rest were air dried. The alcohol fixed slide was stained by haematoxylin and eosin (H&E) stain for cytological examination. For the air dried slides, one was for Ziehl Neelsen (ZN) staining to look for Acid Alcohol Fast Bacilli (AAFB) and the other slides were stained by Diff Quick stain for cytological examination at a later time. Cytology and histology was performed by a senior and experienced pathologist who has been doing similar work using the set criteria outlined below. For each of the specimen AAFB microscopy and cytology were done first and later histology was done with blinding to the first set of results. In each case a summary of clinical information was made available to the pathologist.

For quality control 10% of the specimen were randomly selected and reviewed by an independent senior pathologist. Histological diagnosis of TB was made basing on at least one of the three histological findings including: caseous necrosis, fibrosis or granulomas.¹¹ Diagnosis of KS was based on finding clusters or single spindle cells and or plump cells in a background of numerous red blood cells and mature lymphocytes.¹² The Reed Sternberg cells and "popcorn" cells formed the basis for diagnosis of Hodgkin's disease. Reactive adeni-

tis was based on finding mixed population of lymphoid cells on histology of the lymph node tissue. The cytological diagnosis of toxoplasmosis was made based on seeing tangible body macrophages and a background of mature lymphocytes, predominantly small lymphocytes.

Statistical analysis

All data was double entered into Epi-Info version 6.04 and analysed using SPSS 10.0 software.

Descriptive statistics were used to summarize baseline characteristics of the study patients, into means, medians, proportions, and standard deviations. The diagnostic yield of the 2 procedures was compared by diagnosis. To determine the diagnostic accuracy of FNAC in the evaluation of aetiology of cervical lymphadenopathy; we estimated the sensitivity, specificity; negative and positive predictive values using histology as the gold standard.

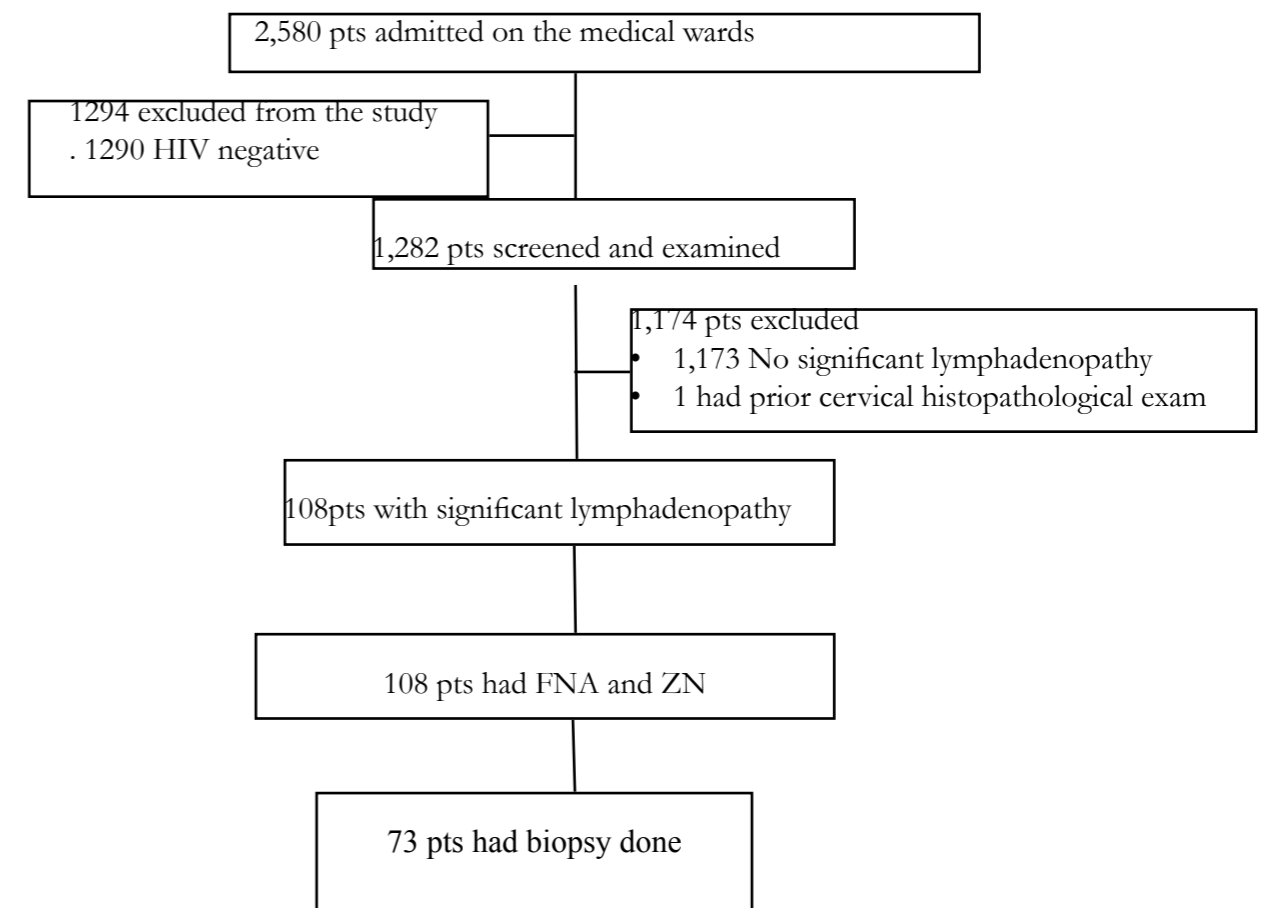
Ethical approval

The study was approved by the Faculty of Medicine Research and Ethics Committee of the School of Medicine, Makerere University College of Health Sciences and the Uganda National Council for Science and Technology and written informed consent was obtained from all study participants.

Results

Between February 2007 and June 2007, 1286 patients with HIV infection were admitted to medical wards at Mulago National Referral Hospital in Kampala and screened for enrolment (see figure 1). Among the enrolled 108 patients, the mean age was 33 years (Range 18-60 years) and 59% were men. Thirty nine patients (36.2%) had generalized lymphadenopathy while sixty nine (63.9) had only cervical lymphadenopathy.

Figure 1 Patient Flow Chart



Abbreviations: HIV, Human Immunodeficiency virus; Pts-patients, ZN, Zeibl Neelsen stain

Seventy four patients (68.5%) had tested for HIV within the past one year and with 107 (99.1%) presenting as advanced WHO HIV stage III and IV. The mean CD4 count for the study patients was 83 (range, 22-375) cells /mm³. Up to 106 (98.1%) were quite ill with

a Karnofsky performance status of less than 50% and only 62(57.4%) were receiving cotrimoxazole prophylaxis (table 1). Only 22 (20%) were receiving ART, with stavudine, lamuvidine and nevirapine (75%) commonest ART combination according to the guidelines at that time.

Table 1: Baseline characteristics of study participants with cervical lymphadenopathy in Uganda

Characteristic	N=108
Men, number (%)	64 (59.3)
Mean age in years, mean (range)	33 (18-60)
Mean BMI, Kg/m ² , mean (range)	23.7(17-34)
Lymphadenopathy, number (%)	
Cervical only	69 (63.9)
Generalized	34 (36.1)
Respiratory examination, number (%)	
Normal	87(80.6)
Abnormal (crackles/pleural effusion)	21(19.4)
Period since diagnosis of HIV, number (%)	
< 1year	74(68.5)
1-5years	27(25.0)
>5years	7 (6.5)
WHO stage, number (%)	
Stage 1 &2	1(0.9)
Stage 3&4	107(99.1)
CD4 cells/mm ³ , mean (range)	83(22-375)
Receiving cotrimoxazole, number (%)	62(57.4)
Receiving ART, number (%)	22(20.0)
Karnofsky score, <50, number (%)	106(98.1)

Abbreviations: SD-standard deviation, BMI-Body mass index, ART- antiretroviral therapy

Aetiology of cervical lymphadenopathy

Out of 108 patients, only 73 had both fine needle aspiration and biopsy done, while 35 (32.4%) had only fine needle aspiration, as the nodes were not easily accessible for biopsy because they were too deep or were fluctuant.

On FNAC diagnosis was 65.7% tuberculosis, 10.2% Kaposi's sarcoma, 7.4% non specific reactive adenitis, 3.7% Hodgkin's lymphoma and one patient each 0.9% for NHL, toxoplasmosis and metastatic carcinoma (table 2). Diagnosis by histology showed; 79.5% tuberculosis, 13.6% Kaposi's sarcoma, 4.1% non specific reactive adenitis, 1.3% non Hodgkin's lymphoma and

1.3% secondary metastatic carcinoma (table 2). FNAC was not able to come up with a conclusive diagnosis in 9.3% of the samples obtained. Among the 58 patients with histological diagnosis of TB, only 35 (60.3%) had a positive ZN on FNA and among the 71 patients with cytological diagnosis of TB, only 48 (67.6%) had a pos-

itive ZN. KS was seen at a significantly higher CD4 (153, SD 177) cells/mm³ as compared to tuberculosis whose mean CD4 cell counts was 70 (SD, 97) cells/mm³ (p-value, 0.034). None of the selected samples for quality control (10%) had a disagreement with the original diagnosis.

Table 2. Diagnosis of cervical lymphadenopathy and mean CD4 among HIV-infected patients in Uganda

Diagnosis	FNAC			Histology		
	Freq	%	Mean CD4 (+/- SD)	Freq	%	Mean CD4 (+/- SD)
Tuberculosis	71	65.7	68 (100)	58	79.5	70 (97)
KS	11	10.2	147(168)	10	13.6	153 (177)
Reactive	8	7.4	114 (92)	3	4.1	57 (65)
HD	4	3.7	113 (88)	0	0	NA
NHL TOXO	1	0.9	NA	1	1.3	NA
Metastatic ca.	1	0.9	NA	0	0	NA
Non diagnostic	1	0.9	NA	1	1.3	NA
Missing results	10	9.3	79 (79)	0	0	NA
	1	0.9	NA	0	0	NA
Total	108	100		73	100	

Abbreviations: FNAC-Fine needle aspiration cytology; HD-Hodgkin's disease; KS-Kaposi Sarcoma; NA- Not applicable; NHL-Non Hodgkin's Lymphoma; Toxo-toxoplasmosis

Plates A to D (figure 2) show the histological diagnosis of the four commonest causes of cervical lymphadenopathy. Of the 71 patients diagnosed with TB on FNAC, only 48 patients (67.6%) had a positive ZN

smear. All patients had caseous necrosis and 46 (64.8) had granulomas. Seventy seven percent of the patients with lymphadenopathic KS had mucocutaneous lesions.

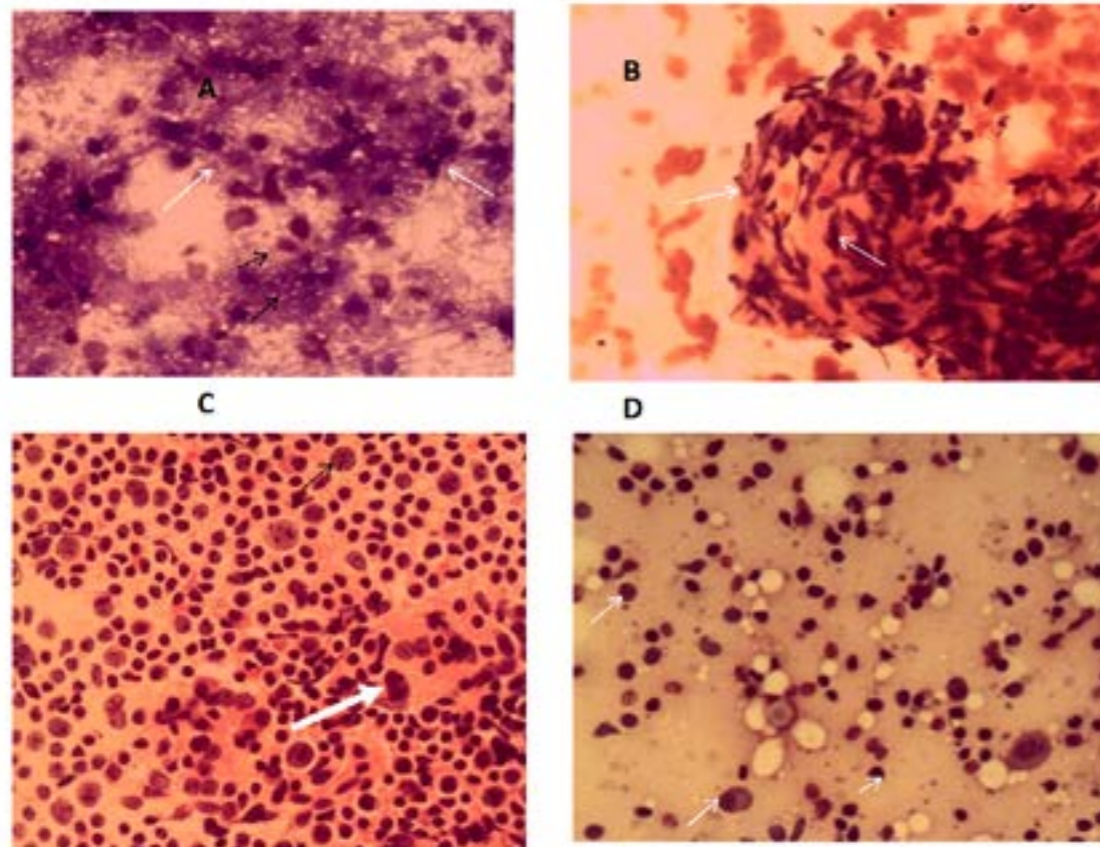
Figure 2 : FNAC PLATES

A FNAC of cervical lymph node from a 28 year old female showing epithelioid cell granulomas (white arrows) and caseous necrosis (black arrows). (Diff Quic stain. Magnification x 40).

B FNAC from cervical lymph node of a 24 year old male showing clusters of spindle cells (white arrows). (H&E stain. Magnification x 40).

C FNAC of a cervical lymph node showing Reed-Stenberg cells (white arrow) and popcorn cells (black arrow) from a 26 year old female patient with Hodgkin's disease. (H&E stain. Magnification x 40).

D FNAC from a cervical lymph node of a 26 year old HIV positive female patient with a reactive node. Note the different stages of lymphocyte maturation (arrows). (Diff Quic stain. Magnification x 40) FNAC-fine needle aspiration cytology; H&E- Hematoxylin and Eosin



Duration and complications of FNA procedure

The FNA procedure was shorter to perform as compared to the biopsy. FNA took a maximum of five minutes to be completed before processing. Processing the slide took another average of ten minutes in the ward side laboratory. We recorded no immediate complications with the FNA and none was reported in the period between doing the procedure and returning of the patients results. To carry out an open lymph node biopsy required surgical instruments, local anaesthetic agent, surgical sutures and draping towels. The minimum time which was taken to complete an open lymph

node biopsy was 20 minutes and processing the specimen required a minimum time of 24 hours. However no immediate complications were reported by any patient following the biopsies from the time of biopsy to the time of returning the histology results.

Diagnostic accuracy of FNAC

FNAC notably had a high diagnostic accuracy with a sensitivity of 93.1%, specificity of 100%, positive predictive value (PPV) of 100% and negative predictive value (NPV) value of 79.9% for TB and sensitivity of 80%, specificity of 98.4%, PPV of 88.9% and NPV of 98.9%

for KS when compared to histology. However, the diagnostic accuracy was relatively low with a sensitivity of

66.7% and a Kappa score of 0.65 for the diagnosis of reactive adenitis (table 3).

Table 3. Sensitivity, specificity, PPV, NPV, kappa statistics of FNAC compared to histology among HIV-infected patients in Mulago Hospital, Uganda

Diagnosis	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Kappa score
TB	93.1	100	100	78.9	0.85
Reactive	66.7	98.5	66.7	98.5	0.65
KS	80	98.4	88.9	96.8	0.82

TB-tuberculosis, KS- Kaposi's sarcoma, PPV-positive predictive value, NPV-negative predictive value

Overall, 65(89%) of FNAC findings were in agreement with the histology results for the same patients. For the other diagnoses the numbers were too small, to determine the accuracy of FNAC. The non diagnostic FNACs were 10 and the main reason for these was insufficient sample material from FNA according to the pathologist. These non diagnostic FNAs were encountered in instances where a bloody aspirate was got. Two of these bloody stained aspirates, later turned out to be KS on lymph node biopsy. The remaining eight non diagnostic FNAs, a diagnosis was not made at all, since even the biopsy was not done due to inaccessibility of the nodes. One patient had both TB and KS found in one lymph node on FNAC.

Discussion

Diagnostic accuracy

Overall FNAC diagnosis was in agreement with histological diagnosis in more than four fifth of the patients, which is quite high and shows that FNAC is generally a very accurate diagnostic procedure in HIV-infected patients with cervical lymphadenopathy. This was comparable to earlier studies done elsewhere.^{13,14} FNAC was able to come up with a diagnosis in 83% (29/35) patients where biopsy was not possible, emphasizing the diagnostic utility of FNAC even when biopsy is difficult.¹⁵

FNAC was found to be a highly accurate method in the diagnosis of TB; with a sensitivity of over ninety percent and a specificity of 100%. This compares favorably with other studies done elsewhere in the developing world where TB is endemic.^{10,16} These findings were different from studies done in the developed world where

TB is not endemic, where FNA was found to have a very low sensitivity of 46% in the diagnosis of TBLN.¹⁷ The ZN positive rate was over two thirds which falls within the reported range of (10-77%).^{1,2,17} This emphasizes the fact that a negative ZN on FNA does not rule out tuberculosis.

There were no false positive diagnoses made on fine needle aspiration for the diagnosis of tuberculosis; however there were four false negatives when compared with histology the gold standard. This is comparable with what previous studies found.^{13,18} This study had a lower false negative rate in TB diagnosis when compared to a study by Aljafari et al in Sudan where he found a false negative rate of 38% using a bigger gauge needle.¹⁹ The difference, probably can be attributed to the differences in sizes of needles used, since the bigger the needle the higher the chances of haemorrhage distorting the cytological picture. There was an excellent kappa agreement of 0.85 between FNAC and histology results in the diagnosis of tuberculosis. This therefore means that results of FNAC are quite comparable to results of histology making it quite a useful method in diagnosis of TB adenitis even in the absence of histology. This therefore means that it will be a very useful method if employed for use for TB diagnosis in Uganda. FNAC was also highly accurate in the diagnosis of KS and this was comparable to what Bates et al found.¹⁸

Diagnosis of reactive adenopathy with FNAC had a relatively low sensitivity compared to other aetiologies like TB and KS. This clearly depicts the diagnostic pitfalls of FNAC in diagnosis of reactive adenopathy as also reported by Reid et al.²⁰ The number of patients with

reactive adenopathy was however quite small, and this may have affected the result we got. Moreover, reactive adenitis has been questioned as a diagnosis²¹. For the other aetiologies of cervical lymph nodes found in our study, that is NHL and secondary metastatic carcinoma, the numbers were too small to determine the diagnostic accuracy of FNA in their diagnosis. One patient had both TB and KS found in one lymph node on FNAC. A similar finding was reported by Hayes in a suspected HIV patient case report.²² This re-emphasizes the possibility of two diagnoses in one node, especially in HIV positive patients as has been reported elsewhere.^{16,22} This dual aetiology however was discovered on FNAC in this study, and this was possible because more than one pass was made through the lymph nodes at different points.

Our study has several strengths. Our observations were drawn after screening over 1,200 patients in one of only two national referrals hospitals in Uganda. The hospital admits patients from most of the HIV care centers drawing a diverse population of HIV patients. We were unable to do lymph node biopsies in 35 patients who had cervical lymphadenopathy, since some lymph nodes were very deeply seated and not easily accessible for biopsy while in three patients, the nodes were fluctuant and not feasible for open biopsy. Biopsying a fluctuant lymph node carries a great risk of fistula formation.^{23,24} For such patients fine needle aspiration may be the only means of making the diagnosis and guide therapy with great accuracy according to our study. The majority of patients were below the fourth decade and this made the likelihood of finding other aetiologies less likely. In as much as this may be in agreement with the current demographics of HIV infection, these results may not be applicable to the older population of patients with HIV. Mycobacterial culture and PCR on the FNA material were not done for TB diagnosis. These may have improved on the diagnostic accuracy of FNAC and should be included in future studies.

Aetiology of cervical lymphadenopathy

Our study found tuberculosis to be the commonest cause of cervical lymphadenopathy among the study patients. This was similar to what was found in previous studies done in Uganda and other developing countries.²⁵⁻²⁷ The percentage of TB was higher in this study at 69.4% as compared to Adrigwe's study done in

Mulago hospital, where it was 47.5%. This difference may be explained by the fact that this was a slightly different study population. Adrigwe studied a population of both HIV positives and negative patients, while only HIV positives were included in our study. It has been demonstrated that advanced HIV infection may increase the diagnostic yield of FNA. This has been attributed to reduced immunological capacity of the immune system to clear off the mycobacterium in HIV infected patients.

The second commonest cause of cervical lymphadenopathy was Kaposi's sarcoma causing about a tenth of all adenopathies. This is comparable to the previous studies done.^{13,18,26} Over a third of patients with lymphadenopathic KS (n=10), had mucocutaneous KS as well, which emphasizes the importance of examination of the skin and mucous membranes in HIV positive patients with lymphadenopathy, since it may elucidate on the possible cause of lymphadenopathy.

Non specific reactive lymphadenopathy was the third commonest cause accounting for less than a tenth of all the lymphadenopathies. This was quite different from what Adrigwe found among medical patients with cervical lymphadenopathy, where this accounted for (28.3%) of all aetiologies.²⁶ Other studies elsewhere also differed greatly from the findings of our study, with reactive non specific adenitis occurring more frequently.^{10,13,17,28} This may be explained by the difference in the study populations, the patients in our study were probably more immune suppressed as compared to patients in other quoted studies above, making tuberculosis more likely than reactive adenitis to affect the nodes.

The majority of the patients were very sick with Karnofsky performance status of less than 50. This may be because the study population constituted patients entirely from the medical wards, where patients are generally very sick and confined to bed in most cases. This shows that patients present late for care and may also explain the high mortality rate on the medical wards that has been reported in other studies.^{29,30}

Key messages

- FNAC is safe and accurate in the diagnosis of cervical lymphadenopathic tuberculosis and Kaposi's sarcoma among HIV positive patients with advanced disease.
- Tuberculosis is currently the commonest cause of

cervical lymphadenopathy among HIV patients in Uganda.

- FNAC is still useful in diagnosis of tuberculosis even when microscopy with Ziehl Neelsen (ZN) is negative

Conclusion

In summary, our study shows that tuberculosis is currently the commonest cause of cervical lymphadenopathy among HIV patients who participated in the study. FNAC is an accurate diagnostic method in evaluation of aetiology of cervical lymphadenopathy among HIV positive individuals, especially in the diagnosis of tuberculosis and Kaposi's sarcoma. Moreover, FNA is quite a useful diagnostic test even where lymph node biopsy is not possible. However, a negative FNA on ZN test does not rule out tuberculous adenitis and FNAC is still useful in diagnosis of tuberculosis even when ZN is negative.

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