Pulmonary co-morbidity in HIV-infected sputum AFB smear-negative Ugandan adults

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SUMMARY

Objectives: **To determine the extend of comorbidity present in HIV positive and negative patients with respiratory tract infections.**
Methods: **Descriptive cross sectional study. Between October 2002 and December 2003 88 bronchoscopies were analysed at Mulago teaching hospital.**
Results: **70.5% of the patients were HIV positive with a mean age of 35.1 years. In the HIV positive group, PKS was the most frequent diagnosis made (38.7%), followed by PCP (37.1%) and PTB (14.5%). In the HIV negative group, lung malignancy was the commonest diagnosis found. Ten of the HIV positive patients (16.1%) had two or more pulmonary diseases: two patients had both PCP and PTB, three patients had PKS and PTB, four patients had PKS and PCP, and one patient had PCP, PKS and PTB. When we analysed according to diseases, 30.4% (7/23) of PCP patients had other opportunistic diseases, PKS patients, 30.0% (8/24) and PTB patients, 66.7 % (6/9).**
Conclusion: **The presence of multiple infectious agents may explain why some HIV positive patients with respiratory disease show only temporary clinical improvement. This suggests that one diagnosis may not be enough for HIV patients.**

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Introduction

Even though the frequency of opportunistic respiratory infections is decreasing since the introduction of antiretroviral therapy (ARV), respiratory diseases are still a main cause of mortality and morbidity in HIV infected patients. , In Uganda, where less than 50% of HIV patients who need ARV have access to it, many patients are admitted to hospitals with advanced immunosuppression. We have seen some patients on treatment for Pneumocystis jiroveci pneumonia (PCP) who deteriorate after an initial improvement; some of these patients were later proven to have other pulmonary diseases, such as pulmonary tuberculosis (PTB) or pulmonary Kaposi's sarcoma (PKS). Though the presence of dual or more pathogens in HIV patients has been reported in the early HIV epidemic, , we hardly find literature that demonstrates the severity or prevalence of respiratory co-morbidity in HIV positive patients.

Materials and methods

A descriptive cross-sectional study was undertaken.

Patient selection

Between October 2002 and December 2003, 124 bronchoscopies were performed in the bronchoscopy unit of Mulago teaching hospital in Kampala, Uganda. The patients were referred from inpatients wards and the out patient department of Mulago hospital, and other hospitals. Bronchoscopy was performed on those patients if three sputum smears of Acid Fast Bacilli (AFB) were negative or they could not produce sputum

effectively. All of them agreed to get bronchoscopy examinations.

We selected the patients who had agreed to do HIV serology test. We also analysed the indications for bronchoscopy for the patients.

Bronchoscopy and laboratory examinations

Bronchoscopy with bronchoalveolar lavage (BAL) was done on every patient and a Ziehl Neelsen stain for AFBs was carried out on all BAL fluid samples. Immunofluorescent staining using monoclonal antibodies against Pneumocystis jiroveci glycoprotein was performed on the BAL samples only when the patient was HIV seropositive. Where malignancy was suspected, the washing fluid was taken for cytological studies and endobronchial biopsy was performed.

Results

Demographic data

The number of patients was 88 (46 male, 42 female), of these sixty two patients (70.5 %) out of 88 were HIV seropositive. The mean age of the 88 patients was 40.2 years (range 18 to 79). The mean age of HIV positive group was 35.1 years, and that of HIV negative 52.4 years. 10 patients had a history of taking ARVs.

Table 1. Indications of Bronchoscopy

Indications	HIV (+) group	HIV (-) group
Lung mass/nodule	4	12
Hemoptysis	2	4
Atelectasis	0	4
PTB/Pneumonia	5	4
HIV associated infection/PKS	49	0
Others	2	2
Total No.	**62**	**26**

In the HIV seropositive group, 79.0% of the subjects were referred for bronchoscopy because attending doctors had thought they had HIV associated opportunistic diseases, such as PCP or PKS. While the most common indication of bronchoscopy for HIV seronegative group was a lung mass on chest x-ray (46.2%).

In the HIV positive group, PKS was the most frequent diagnosis made in 38.7%, followed by PCP (37.1%) and PTB (14.5%). In the HIV negative group, lung malignancy was the commonest diagnosis found. Among these a histological diagnosis of squamous cell carcinoma was found more often than adenocarcinoma.

Table 2. The diagnoses of pulmonary diseases confirmed by bronchoscopy.

Diagnosis	HIV positive (62)	HIVnegative (26)
PKS*	24 (38.7%)	0
PCP	23 (37.1%)	0
PTB	9 (14.5%)	2 (8.0%)
Suppurative lung disease**	4 (6.5%)	3 (11.5%)
Squamous cell carcinoma	0	6 (23.0%)
Adenocarcinoma	0	2 (8.0%)
Metastatic carcinoma	0	2 (8.0%)
No diagnosis	10 (16.1%)	11 (42.3%)

** The diagnosis was made when Kaposi's sarcoma (KS)-plaques were found on bronchoscopy and KS was confirmed by biopsy specimen from other sites such as skin or oral mucosa.*

*** The diagnosis was made when pus-like secretion was found in the airway, but AFBs were not found while many bacteria were found on the stain.*

In the HIV seropositive group 10 (16.1%) patients had two or more pulmonary diseases: two (3.2%) patients had both PCP and PTB, three (4.8%) patients had PKS and PTB, four (6.4%) patients had PKS and PCP, and one (1.6%) patient had PCP, PKS and PTB. In contrast, the HIV seronegative group had no co-morbidities.

Table 3. Co-morbidity of respiratory diseases in patients presenting to the bronchoscopy unit

Co-morbidity	HIV positive group	HIV negative group
	10 (16.1%)	0 (0%)
PCP + PTB	2	0
PKS + PTB	3	0
PKS + PCP	4	0
PCP + PKS + PTB	1	0

When we analysed according to diseases, 30.4% (7/23) of PCP patients had other opportunistic diseases, PKS patients, 30.0% (8/24) and PTB patients, 66.7 % (6/9). (Table 4)

Table 4. The prevalence of co-morbidity in each disease

Diagnosis	Patients number	Number of Co-morbidity
PKS	24	8 (33.3%)
PCP	23	7 (30.4%)
PTB	9	6 (66.7%)

Discussion

HIV sero-status of patients

In this study, 70.5% (62/88) of patients who were transferred for bronchoscopy were HIV seropositive. Even though this percentage does not directly reflect HIV seropositivity among patients with respiratory diseases in Uganda, this feature indirectly shows that HIV infection still is a major cause of undiagnosed respiratory illness in clinical practice.

The mean age of HIV positive group was younger than that of HIV negative group. This correlates with national data that the peak of HIV seropositivity is between 20-40 years.

The result of bronchoscopy

In the HIV positive group, PKS was the commonest diagnosis (38.7%), followed by PCP (37.1%) and PTB (14.5%). According to Worodria et al under a similar setting the study findings were different. At that time, the most common diagnosis was PCP (38.6%), followed by PTB (24%), and PKS (11%).

In the current study the prevalence of PTB and PCP was similar to that study, but the prevalence of PKS was much higher. The reason for the high prevalence of PKS is not clear, but this might be due to the increased awareness of medical doctors that PKS is common in KS patients. Therefore, more patients with KS are referred for bronchoscopy to confirm the diagnosis of PKS than before.

PKS

The diagnosis of PKS was made at bronchoscopy when typical violaceous lesions of KS were identified in the endobronchial tree in patients who had KS lesions that was confirmed by biopsy of other sites of the body such as the skin or oral mucosa. In our study, PKS was found in 38.7% of the subjects. The incidence of PKS is difficult to assess because, even with bronchoscopy, the diagnosis is not established in every case. Mitchell and Miller reported that only 45% of cases have endobronchial lesions located at segmental orifices in the main trachea or bronchi where bronchoscope can reach. However, bronchoscopy is still the most useful tool in making the diagnosis of PKS. According to postmortem studies, PKS has been found in 47% of patients with cutaneous KS and 59% of patients dying with AIDS had KS, that was unsuspected premortem in any patient. Therefore, the incidence of PKS in AIDS patients may be approximately 30%. PKS should be considered in the differential diagnosis of all patients with HIV infection presenting with respiratory symptoms.

PCP

The prevalence of PCP in this study was 37.1%. It was similar to Worodria et al 5 that showed 38.6%. In earlier studies, the prevalence of PCP was quite lower than these with range of 5-11%. Those studies most probably showed a lower prevalence of PCP than recent studies because they used other staining methods other than the immunoflorescent stain using monoclonal antibodies that is regarded as the "gold standard".

PTB

In keeping with others studies in Africa, our study shows a high prevalence of TB among sputum AFB smear negative patients. Batungwanayo et al found 23% of the patients with pulmonary disease of unknown etiology had TB in Rwanda12. In Worodria et al study, the prevalence of TB was 24% and the ZN stain for AFB showed positive in 55% of them5. By culture it was possible to identify 45% of patients that were initially AFB smear negative on BAL fluid. We did ZN stain on the BAL fluid but TB cultures were not done. This could explain why the prevalence of TB was not as high as in other studies.

One challenge in making a diagnosis of TB is the reliability of ZN stain. If AFB are identified from sputum or from BAL fluid samples, can we confidently make a diagnosis of PTB? The prevalence of atypical mycobacteria in developed countries is increasing. However, in developing countries where TB is very prevalent, the prevalence of atypical mycobacterial infection is negligible . Worodria et al anaylsed BAL fluid from HIV seropositve group, but found no atypical mycobacterium from the culture.5 Therefore, in programmatic situations recommendations that doctors should start antituberculous treatment based on positive sputum AFB is reasonable.

Pulmonary co-morbidity

The indications for bronchoscopy in table 1 in HIV seropositive and negative groups are presented in table 1. Because the indications for bronchoscopy were different in the two groups, we cannot compare their results. However, the point is very clear that there are pulmonary co-mobidities in the HIV seropositive group while no co-morbidity was observed in HIV seronegative group.

The present study shows that 10 patients (16.1%) had two or more pulmonary diseases: two patients had both PCP and PTB, three patients had PKS and PTB, four patients had PKS and PCP, and one patient had PCP, PKS and PTB.

The presence of pulmonary comorbidity has been reported in Sub-Sahara Africa. Batungwanayo et al 12 reported pulmonary co-morbidity in HIV positive patients. In their study among 14 pulmonary cryptococcosis patients, 2 patients had PTB and one had PKS in addition. Worodria et al reported 5 patients had PCP and PTB, 3 patients PCP and PKS, and one patient PKS and PTB among 83

admitted patients.5 Yoo et al found that 5 patients had PTB, and one patient PCP among 20 PKS patients in Uganda. However, the percentage of co-morbidity in those studies is unclear.

In the present study (Table 4), among patients diagnosed with PCP, 30.4% (7/23) of them had other opportunistic diseases, in PKS patients, 30.0% (8/24) and among PTB patients, 66.7 % (6/9). This implies that pulmonary co-morbidity in HIV patients is not rare.

At the time of this study most HIV positive patients in this study did not have access to ARVs, and CD4 count tests were not routinely available. It was not possible to stratify the diseases pattern according to CD4 counts. However currently there are country-wide efforts to scale up provision of ARVs to eligible HIV positive patients. Furthermore the cost of CD4 count is getting cheaper, so future studies may be able to analyse the different disease patterns according to different CD4 levels.

Due to lack of laboratory diagnostic facilities, we could not investigate the presence or absence of viral or fungal infections. It is very likely that more pulmonary co-morbidities would have been found in patients with HIV if facilities to diagnose those diseases were available.

Conclusion

Pulmonary comorbidity is common in HIV positive patients. The presence of multiple infectious agents may explain why some HIV positive patients with respiratory disease show only temporary clinical improvement. This suggests that one diagnosis may not be enough for HIV patients.

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