



Pulmonary Cryptococcosis Co-existing with Pulmonary Tuberculosis in a Nigerian HIV-infected Patient: A Case Report

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Authors' contributions

This work was carried out in collaboration between all authors. Authors OFN, CAN and GCM did the study design and wrote the protocol. Authors PO, EOO and COUE did the statistical analysis and literature searches while analyses of study was by authors MOI and ABN. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJTDH/2016/25157

Editor(s):

(1) Giuseppe Murdaca, Clinical Immunology Unit, Department of Internal Medicine, University of Genoa, Italy.

Reviewers:

(1) Wagner Loyola, Brazilian Agricultural Research Corporation, Brazil.

(2) Joaquin Cervantes, Red Balloon Group, Inc. El Paso, Tx, USA.

Complete Peer review History: <http://sciencedomain.org/review-history/14128>

Case Report

Received 20th February 2016

Accepted 10th March 2016

Published 12th April 2016

ABSTRACT

Tuberculosis (TB) and cryptococcosis cause severe morbidity and mortality in HIV-infected individuals in sub-Saharan Africa. However, cryptococcosis and TB co-infection is rare. We present a case of pulmonary cryptococcosis co-existing with pulmonary TB in a 42 year old Nigerian woman who had received Highly Active Antiretroviral Therapy (HAART) for about 6 months with CD4 count of 98 cells/mm³. In the second month of HAART, she developed smear positive TB and was commenced on anti-TB therapy. Following initial improvement, she developed new onset cough, low grade fever, weight loss, breathlessness and chest pain. Repeat sputum Acid Fast Bacilli (AFB) was negative but GeneXpert/MTB/Rif detected *Mycobacterium tuberculosis* (MTB) with no

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resistance to Rifampicin. Sputum fungal culture and Indian ink staining confirmed cryptococcosis. The patient was commenced on oral fluconazole therapy; anti-TB and HAART were continued. She subsequently improved but was unfortunately lost to follow-up. Pulmonary cryptococcosis should be considered in the differential diagnosis of severely immunosuppressed HIV-infected patients with chronic respiratory symptoms.

Keywords: Pulmonary; cryptococcosis; tuberculosis; HIV/AIDS; Nigeria.

1. INTRODUCTION

Cryptococcosis is an opportunistic infection caused by *Cryptococcus* organism, an encapsulated fungus. *Cryptococcus neoformans* is the main aetiological agent in the immunocompromised, though other forms such as *C. gatti* may rarely cause infection [1]. In HIV-infected populations, cryptococcosis is a common cause of morbidity and mortality even in the era of Highly Active Antiretroviral Therapy (HAART) [1]. Cryptococcosis in HIV/AIDS most commonly affects the Central nervous system (CNS) and the lungs, although the skin and other sites may be involved [1].

On the other hand, tuberculosis (TB) is by far the commonest opportunistic infection in HIV-infected populations in sub-Saharan Africa [2]. While Pulmonary tuberculosis (PTB) remains dominant in HIV/AIDS, extra-pulmonary disease including CNS involvement occurs more commonly than in the general population.

Incidentally, pulmonary cryptococcosis has similar clinical presentation as pulmonary TB, [1] which may make clinical distinction difficult. This is particularly important in resource-limited settings where facilities for definitive diagnosis of these conditions may be lacking. Although multiple opportunistic infections may occur in immunocompromised patients, co-infection of cryptococcosis and TB is rare. We report a case of pulmonary cryptococcosis co-existing with pulmonary TB in a severely immunosuppressed Nigerian HIV-infected patient on HAART.

2. CASE PRESENTATION

CAN, a 42 year old HIV-infected woman receiving care at Federal Medical Centre (FMC) Owerri, Nigeria. She had received HAART (Zidovudine/Lamivudine/Efavirenz) for about 6 months with current CD4 count of 98 cells/mm³. In the second month of HAART, she developed pulmonary TB and was commenced on anti-TB drugs (Rifampicin/Isoniazid/ Pyrazinamide/ Ethambutol in the first two months and

Rifampicin/Isoniazid in the continuation phase). Diagnosis of TB was based on suggestive clinical/radiological features and positive sputum Acid Fast Bacilli (AFB). She initially improved but in the fourth month of her anti-TB therapy, she presented with new onset productive cough of eight weeks associated with low-grade fever, breathlessness, chest pain and recent weight loss. There was no history of drenching night sweat or haemoptysis. She did not have any history of tobacco use, asthma or chronic obstructive airway disease. She was judged to have good adherence for HAART, anti-TB drugs and cotrimoxazole prophylaxis by pharmacy records and personal report.

On physical examination, she was ambulant, chronically ill-looking and febrile (37.8°C). Other general examination findings were normal. Respiratory examination was only remarkable for tachypnoea (26 breaths/min). Nervous system, abdominal, skin and cardiovascular findings were normal. A presumptive diagnosis of Multidrug Resistant Tuberculosis (MDR-TB) in an HIV-infected patient receiving HAART was made. Differential diagnoses entertained were fungal lung disease and pulmonary malignancy.

Chest radiograph showed patchy opacities and reticulo-nodular shadows in the mid and lower zones bilaterally. Repeat sputum AFB was negative; Sputum Gram staining was negative and no pathogens were isolated from sputum after 24 hours of incubation at 37°C on Nutrient and Blood agar. GeneXpert/MTB/Rif of sputum detected *Mycobacterium tuberculosis* with no resistance to Rifampicin. Mycobacterial culture could not be done due to lack of facilities. Sputum culture on Sabouraud Dextrose Agar (SDA) impregnated with Chloramphenicol revealed light yellow mucoid and convex growth after 24 hours of incubation at 37°C, with a characteristic halo on Indian ink staining in keeping with *Cryptococcus neoformans*. Cerebrospinal fluid (CSF) culture and Indian ink studies were negative for cryptococcal organism and this rules out cryptococcal meningitis.

The diagnosis was modified as pulmonary cryptococcosis in a patient being treated for HIV/TB co-infection. She was administered antifungal therapy using oral Fluconazole 400 mg 12 hourly. HAART, continuation phase anti-TB therapy and Cotrimoxazole prophylaxis were continued. Adherence counseling was re-enforced. After four weeks of Fluconazole therapy, she made remarkable clinical improvement and was scheduled for monthly clinic visits. Unfortunately, she was lost to follow-up in the second month of fluconazole therapy and efforts by the tracking team to trace her were unfruitful.

3. DISCUSSION

Cryptococcus neoformans is an encapsulated yeast-looking fungus that is commonly found in pigeon droppings and soil. Despite the ubiquity of the organism in the environment, human infection is uncommon, except in individuals with cell-mediated immunosuppression as seen in HIV/AIDS, malignancies, prolonged steroid use and immunosuppressive therapy after organ transplant [1]. Following access into man through the respiratory tract, primary infection with the fungus is established in the lungs. From the lungs, haematogenous spread may occur leading to infection in the CNS, the skin/soft-tissues and the urogenital system.

In HIV-infected populations, cryptococcal meningitis, the most common and lethal presentation of the disease, is estimated to occur in 1 million persons annually worldwide, resulting in nearly 625,000 deaths [3]. Most cases of cryptococcosis occur in sub-Saharan Africa where it has become the leading cause of meningitis in HIV-infected adults [3]. Available studies in sub-Saharan Africa suggest that the prevalence of pulmonary cryptococcosis in HIV-infected persons with respiratory symptoms is 10-19%, [4-6] depending on the immune status of the cohorts.

The peculiarity of the case we reported lies in the co-existence of pulmonary cryptococcosis with pulmonary TB. The predisposition of the patient to opportunistic infections is understandable despite the fact that she was receiving HAART bearing in mind that she was still severely immunosuppressed with CD4 count of 98 cells/mm³. Whereas HIV-associated TB can occur at any CD4 cell count, the median CD4 cell count in African cohorts with HIV-associated cryptococcosis

is known to be less than 100 cells/mm³ [2].

Initial diagnosis of PTB in the patient was based on compatible clinical and radiological features and sputum AFB positivity. In resource-limited settings where facilities for mycobacterial culture are often lacking, this is an acceptable means of diagnosis of PTB. Moreover, the initial improvement the patient experienced during the intensive phase of anti-TB therapy partly justifies the diagnosis of TB. Negativity of the repeat sputum AFB in the continuation phase can be explained by sputum conversion which is expected in drug-susceptible TB on completion of the intensive phase. Although the detection of MTB by GeneXpert, a molecular and by far more sensitive diagnostic tool, further strengthens the diagnosis of TB, it also highlights the fact that molecular tests are not advocated for monitoring of TB treatment response considering that they will remain positive despite sputum conversion [7]. At the point we observed new onset respiratory symptoms, the first consideration was MDR-TB which is logical but this was excluded by the absence of Rifampicin resistance on GeneXpert.

Although PTB and pulmonary cryptococcosis are difficult to distinguish clinically, the new onset symptoms of our patient are similar to clinical presentations reported in HIV-infected patients with pulmonary cryptococcosis elsewhere [1,4]. The most frequent symptoms in 15 Ugandan cohorts were cough (100%; with median duration of 4 weeks), fever (93%), weight loss (93%), chest pain (67%) and breathlessness (63%) [4]. Our patient had all the 5 symptoms. The most common chest radiographic patterns in Ugandan cohorts were interstitial infiltrates (29%), lobar consolidation (21%) or a mixed pattern (21%). Our patient had a mixed pattern. The diagnosis of cryptococcosis in our patient was based on sputum fungal culture and Indian ink findings. Fungal culture is the gold standard for diagnosis of cryptococcosis. The actual onset of pulmonary cryptococcosis in this patient is difficult to say. One possibility is that latent cryptococcal infection in the patient was unravelled as a form of immune reconstitution inflammatory syndrome (IRIS) following few months of ART. Unlike TB-IRIS and pneumocystis-IRIS which tend to occur within days to weeks of starting ART, cryptococcal-IRIS usually occurs later in the course of ART [8] which might have been the case in our patient. Another possibility is that the patient acquired cryptococcal infection while on

HAART bearing in mind that she was severely immunosuppressed. The presence of TB could have also increased her predisposition to other pulmonary opportunistic infections.

In the literature, co-infection of cryptococcosis and TB is rare. However, few cases have been reported [9,10]. In a 14 year retrospective review at a University hospital in Taiwan, Huang et al. [8] found 23 patients diagnosed with cryptococcosis and TB co-infection. Eleven (48%) were HIV-infected. Constitutional symptoms, particularly fever and weight loss, were the most common presenting symptoms. The majority (83%) of the patients made a good recovery following dual antifungal and anti-TB therapy. Three mortalities at the 1-year follow-up were recorded, which the authors attributed to a delay in diagnosis and treatment of the co-infection. Singh et al. [9] reported two cases of concurrent cryptococcal meningitis and tuberculosis HIV infected persons in India.

The major learning point in this report is that the possibility of pulmonary cryptococcosis should be entertained in HIV-infected patients with respiratory symptoms especially those who have severe immunosuppression. In Uganda, among the 15 (out of 132) HIV-infected patients diagnosed with have *C. neoformans* following fungal culture of bronchoalveolar lavage, none of them were suspected to have pulmonary cryptococcosis on admission. The conditions suspected were mainly PTB and bacterial pneumonia and all had received antibiotics for presumed bacterial pneumonia.

The limitations and challenges we experienced should be highlighted. The baseline CD4 count of the patient was missing in the records which made it difficult for us to determine her level of immune restoration after 6 months of HAART. We were unable to perform sputum Mycobacterial culture for our patient due to lack of facilities. By far the most unfortunate challenge was the loss of the patient to follow-up despite efforts to track her using the contact/phone details she supplied at the time of enrolment. The possibility of death as an outcome in this patient cannot be excluded.

4. CONCLUSION

Pulmonary cryptococcosis should be considered in the differential diagnosis of severely immunosuppressed HIV-infected patients with chronic respiratory symptoms. In those being managed for commoner conditions such as PTB,

lack of clinical improvement or reappearance of respiratory symptoms following initial improvement should raise the index of suspicion for other opportunistic diseases such as cryptococcosis. There is need to strengthen the tracking system for HIV-infected patients being managed on out-patient basis for potentially life-threatening conditions.

CONSENT

All authors declare that written informed consent was obtained from the patient's relative for publication of this paper but without any image.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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