Research Article

Tuberculous meningitis and cryptococcal meningitis co-infection in hospitalised patients in Durban, Kwa Zulu Natal (KZN), South Africa

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Abstract

Background: Cryptococcal meningitis (CCM) and tuberculous meningitis (TBM) co-infection has been previously described, although the diagnosis is rare. This may be due to the paucibacillary nature of TBM and the difficulty in diagnosing these conditions due to the overlap of symptoms and cerebrospinal fluid (CSF) findings. This study is aimed to determine the frequency and outcome of TBM and CCM co-infection in hospitalised patients.

Methods: A retrospective review of routine laboratory and clinical records of patients with TBM and CCM co-infection at four regional hospitals in a single metropolitan district in Durban, South Africa was conducted between 1st January 2005 and 31st December 2009.

CSF Tuberculosis(TB) data at Inkosi Albert Luthuli Central Hospital's TB culture laboratory was the starting point for identifying CSF TB culture-positive cases. CSF microbiology laboratory data at each identified hospital study site were then reviewed for this retrospective analysis.

All adult patients whose CSF yielded positive TB cultures were included in this study. These positive *Mycobacterium tuberculosis* (MTB) samples were then matched with CSF samples positive for cryptococcosis, confirmed by cryptococcal latex agglutination test (CLAT), India ink test or culture. A chart review of dual-infected cases was then conducted.

Results: 418 patients were identified based on the gold standard of the time, namely positive CSF TB culture extracted from laboratory data at each study site. Nucleic acid amplification testing was not available during the study period. A total of 15 patients had dual infection, with 10 patients confirmed to be human immunodeficiency virus (HIV) infected. The HIV statuses of the other 5

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patients were unknown but they were clinically immunocompromised. The prevalence of dual infection was 15/418 cases (3.6%). Twelve of the 15 patients were diagnosed with TBM posthumously with an in-hospital mortality of 80% (12/15). Despite the age of the data set, the study remains valid and relevant due to the rarity of TBM and CCM co-infection.

Conclusion: In this study, we found that dual infection of the meninges with *Mycobacterium tuberculosis* and *Cryptococcus neoformans* in HIV-infected patients is rare. However, the diagnosis may often be missed or not considered initially. Underdiagnosis and possible delay in diagnosis of dual infection may result in patients not being treated appropriately and adequately, leading to increased morbidity and mortality.

Keywords: *Cryptococcal meningitis, TB Meningitis, Co-infection*

Introduction

According to the South African National HIV prevalence, incidence, behavior, and communication survey in 2017, the prevalence of human immunodeficiency virus (HIV) in South Africa was estimated to be 14.0%, translating to 7.9 million people living with HIV.[1] Among the medical conditions associated with the highest mortality risk in hospitals in Africa, meningitis is the leading cause of death.[2] Cryptococcal meningitis (CCM) is the most common causative pathogen in advanced HIV infection, especially in those with low CD4 counts.[2] Approximately 250,000 cases of cryptococcosis were recorded in 2014, which accounted for 15% of deaths associated with HIV.[3] Tuberculous meningitis (TBM) is the second most common cause of HIV-associated meningitis.[1] TBM is difficult to diagnose due to its similar clinical presentation to other forms of meningitis.[2] Diagnostic challenges often lead to treatment delays and subsequent mortality.

A study in Cape Town reported that TBM was present in 27% of hospitalised HIV-infected patients admitted with meningitis.[4] TBM presents as subacute meningitis and may present clinically as TBM alone, or as disseminated TB.[5] The clinical presentations of both CCM and TBM are very similar.[4] Patients can present with headaches, neck stiffness, seizures, altered sensorium and focal neurological signs. CSF findings are also very similar in TBM and CCM with lymphocytic predominance, elevated protein and low glucose.[6]

Although the cryptococcal latex agglutination test (CLAT) is highly sensitive and specific, with very few false positives and negatives, CSF culture remains the definitive diagnostic test.[7] CLAT may remain positive in the serum and CSF for an extended period.[7] Thus, CLAT is of limited use when evaluating patients who have had CCM and presenting again with meningitis. In contrast, the rapid diagnosis of TBM remains a significant challenge for both clinicians and microbiologists due to the extremely poor yield of acid-fast bacilli in microscopy of CSF samples and the lack of reliable TB serological or molecular tests.[7] An analysis of 18 Xpert® MTB/RIF studies for the diagnosis of extrapulmonary tuberculosis by Palacios *et al*. (2014) found that the pooled sensitivity for extrapulmonary tuberculosis was 80.5% with a 95% confidence interval (CI), 59.0% to 92.2% when compared with traditional culture and 62.8% when compared with the composite reference standard (CRS).[7] The reference standards were mycobacterial culture or a composite reference standard (CRS) defined by the study authors of the individual studies.[7]

Clinicians in our setting base their treatment regimen on the results of CLAT or India ink stain of CSF. If positive, patients are started on treatment for cryptococcal meningitis. However, it is well recognised that if a patient had previous CCM, the CLAT, and India ink may remain positive for an extended period. Patients who present with new signs suggestive of meningitis may well have TBM. Due to the high TB burden, some patients may be co-infected with both organisms. Dual infection with both TBM and CCM have been documented. A study in Taiwan demonstrated that co-infection in the brain is the second most common site after the lung.[8] A study published in 1998, conducted on mineworkers in rural South Africa, revealed that 2 of 7 (<30%) patients with HIV and suspected meningitis had co-infection with tuberculosis and cryptococcosis.[9]

Wong *et al*., 2012, found at autopsy that 62% of HIV-infected patients with mycobacterial infection had multiple infectious causes of death, including cryptococcosis.[10] However, most of the available literature on co-infection of TB in cryptococcal meningitis amongst HIV-infected patients is limited to series of cases and reports.[11,12,13] A retrospective study by Britz *et al*. (2016) described the epidemiology of meningitis by testing CSF among adults in the Gauteng province in South Africa. They noted cryptococcal meningitis, tuberculous meningitis and pneumococcal meningitis accounted for 62.3% (n = 7,406), 24.6% (n = 2,928) and 10.1% (n = 1,197) of cases respectively over a four-year period.[14] A total of 112 cases (0.9%) of mixed aetiology occurred, of which 95 were cryptococcal and tuberculous meningitis.[14]

The Cryptococcal Optimal Antiretroviral therapy Timing (COAT) Trial, a multisite randomized trial conducted on the management of TBM and CCM by Boulware *et al.(*2014) showed that deferring antiretroviral therapy (ART) until 5 weeks after the start of amphotericin therapy improved the survival of patients with CCM, as compared to initiating ART at 1-2 weeks.[15] Early administration of ART also did not appear to be beneficial in the treatment of HIV-associated TBM. The outcomes and consequences of CNS infections such as cryptococcal and tuberculous meningitis differ from those of other AIDS-related opportunistic infections, in that early administration of ART can be detrimental in CNS infections as it predisposed to immune reconstitution inflammatory syndrome (IRIS).[15]

The Adjunctive Sertraline for the Treatment of Cryptococcal Meningitis (ASTRO-CM) randomised clinical trial by Rhein *et al.* (2016), described an improved rate of fungal clearance from the CSF, combined with acceptable concentrations and the additive effects of sertraline used in combination with fluconazole *in vitro,* suggesting that sertraline may be a useful adjunct for the treatment of cryptococcal meningitis with further prevention of paradoxical cryptococcal IRIS and relapse.[16]

To the best of our knowledge, the presence of dual infection with TBM and CCM has not been well described. This study aimed to describe the frequency and outcome of TBM and CCM co-infection in hospitalised patients and to review the diagnostic and therapeutic processes during hospitalisation in the public health sector in Durban, South Africa.

Methods

Retrospective data from the laboratory and clinical records of patients were reviewed for CCM in those with culture-proven TBM in CSF. The patients were admitted from 1 January 2005 to 31 December 2009 at regional hospitals in the Durban Metropolitan Complex, South Africa. All adult

patients who had positive TB cultures from samples of CSF and were positive for CCM either by India ink test, CLAT or culture were included in the study. Patients with incomplete medical records i.e. CSF results or other data were not available, were excluded.

CSF TB data at Inkosi Albert Luthuli Central Hospital TB Culture Laboratory, the only TB culture laboratory in Kwa Zulu Natal was the starting point for identifying CSF TB culture-positive cases. CSF microbiology laboratory data at each identified hospital study site were then reviewed

All adult patients with CSF samples positive for TB culture were included. These positive MTB samples were then matched with CSF samples which were positive for cryptococcosis by CLAT, India ink or culture. Variables analysed included the age, sex, HIV status, CD4 count, HIV viral load and CSF chemistry and microbiology.

A chart review of the dual-infected cases was then conducted. TBM and CCM infection were concurrent to the best of our knowledge.

Statistical Analysis

Data was collated on a Microsoft® Excel spreadsheet and was then analysed using SPSS software version 24.

Results

Table 1: Number of patients per hospital

	Hospital A	Hospital B	Hospital C
CSF positive TB culture	164	236	140
Duplicate files	20	10	9
Patients <18 years old	8	12	7
File lost	0	56	0
Total patients included in study	136	158	124
Grand Total 418			

A total of 418 patients were identified with confirmed TB meningitis between 1st January 2005 and 31st December 2009 (Table 1), with 15 patients having dual infection (3.5%).

Amongst the patients with dual infection, females were comparatively more than males (6 males vs 9 females). The age range of the study subjects was between 14 and 56 years with the mean age being 37 years. The most common symptoms described were headaches (86.6%), fever (33.3%), photophobia (33.3%) and disturbances in the level of consciousness (26.6%). Several patients also reported a productive cough (40%), loss of appetite (33.3%) and loss of weight (33.3%) as shown in Table 2.

The median CSF neutrophil count/µL was 0, and lymphocyte count/µL was 44, whilst the median CSF glucose and proteins was 0.8 mmo/l and 0.83 g/L in patients with TBM and CCM co-infection respectively.

Ten of the fifteen patients with dual infection were known to be HIV positive at the time of admission, with the remaining five presumed to be HIV infected and not immunosuppressed from another condition. Six of the ten patients had CD4 counts of < 250 cells/µL and CD4 count was not available for 4 patients.

Table 2 and 3a-c depict the profiles of the patients encountered with dual infection:

Table 2: Summary of patients with dual infection: demographics and symptoms

	Age	Sex	HIV status	Presenting complaint	HIV treatment
Patient 1	27	Female	Positive	Cough, constitutional symptoms, headache	No
Patient 2	23	Female	Positive	Cough, constitutional symptoms, vomiting	No
Patient 3	31	Female	Unknown	Cough, constitutional symptoms headaches, diarrhoea,	No
Patient 4	38	Female	Unknown	Cough, constitutional symptoms, headaches, vomiting	No
Patient 5	37	Male	Positive	Headaches, drowsiness, constitutional symptoms	Yes
Patient 6	43	Male	Positive	Headaches, photophobia, seizures, diarrhoea	Yes
Patient 7	24	Female	Positive	Headaches, neck pain, vomiting	Yes
Patient 8	29	Female	Unknown	Headaches, photophobia	No
Patient 9	38	Male	Unknown	Headaches, confusion	No
Patient 10	46	Male	Positive	Headache, photophobia, vomiting, diarrhoea	No
Patient 11	14	Male	Unknown	Cough, constitutional symptoms, diarrhoea, vomiting	No
Patient 12	56	Female	Positive	Headache, vomiting, confusion, diarrhoea	Yes
Patient 13	24	Male	Positive	Headaches, photophobia, blurred vision, constitutional symptoms, cough	Yes
Patient 14	33	Female	Positive	Headache, nausea, vomiting,	Yes
Patient 15	26	Female	Positive	Lower limb weakness, headaches, constitutional symptoms	Yes

Table 3a: Investigations of patients with dual infection (Patients 1-5)

	CD4 T cells/µL	CSF		CSF TB CULTURE	Chest radiography	Neuroradiology findings
Patient 1	**Unknown**	**CSF:** **Neutrophils/µL** **Lymphocytes/µL** **Glucose mmol/L** **(serum glucose mmol/L)** **Protein g/L** **CLAT**	 **22** **10** **1.1** **(4.4)** **0.37** **Positive**	**Positive**	**Bilateral infiltrates on chest radiography**	**Not available**
Patient 2	**Unknown**	**CSF:** **Neutrophils/µL** **Lymphocytes/µL** **Glucose mmol/L** **(serum glucose mmol/L)** **Protein g/L** **CLAT**	 **0** **4** **0.7** **(5.5)** **0.62** **Positive**	**Positive**	**Infiltrates in keeping with miliary TB on chest radiography**	**Not available**
Patient 3	**Unknown**	**CSF:** **Neutrophils/µL** **Lymphocytes/µL** **Glucose mmol/L** **(serum glucose mmol/L)** **Protein g/L** **CLAT**	 **0** **4** **0.7** **(3.5)** **0.62** **Positive**	**Positive**	**Nodular shadowing in keeping with TB**	**Not available**
Patient 4	**Unknown**	**CSF:** **Neutrophils/µL** **Lymphocytes/µL** **Glucose mmol/L** **(serum glucose mmol/L)** **Protein g/L** **CLAT**	 **0** **94** **2.3** **(5.7)** **0.83** **Positive**	**Positive** **MDR TB**	**Normal chest radiograph**	**Not available**
Patient 5	**Unknown**	**CSF:** **Neutrophils/µL** **Lymphocytes/ µL** **Glucose mmol/L** **(serum glucose mmol/L)** **Protein g/L** **CLAT**	 **0** **0** **0.3** **(6.0)** **1.07** **Positive**	**Positive**	**Chest radiograph not available**	**CT brain: Hydrocephalus noted**

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Table 3b: Investigations of patients with dual infection (Patients 6-10)

	CD4 T cells/µL	CSF		CSF TB CULTURE	Chest radiography	Neuroradiology findings
Patient 6	**74**	**CSF:** **Neutrophils/µL** **Lymphocytes/µL** **Glucose mmol/L** **(serum glucose mmol/L)** **Protein g/L** **CLAT**	 **70** **170** **0.6** **(5.8)** **3.9** **Not done**	**Positive** **MDR TB**	**Chest radiograph showed right upper lobe fibrosis**	**CT brain: Age-inappropriate cerebral atrophy**
Patient 7	**Unknown**	**CSF:** **Neutrophils/µL** **Lymphocytes/µL** **Glucose mmol/L** **(serum glucose mmol/L)** **Protein g/L** **CLAT**	 **0** **250** **0.7** **(5.0)** **4.59** **Positive**	**Positive** **MDR TB**	**Chest radiograph not available**	**Not available**
Patient 8	**Unknown**	**CSF:** **Neutrophils/µL** **Lymphocytes/µL** **Glucose mmol/L** **(serum glucose mmol/L)** **Protein g/L** **CLAT**	 **8** **214** **0.9** **(4.8)** **2.24** **Positive**	**Positive** **XDR TB**	**Chest radiograph not available**	**CT brain: basal meningeal enhancement**
Patient 9	**Unknown**	**CSF:** **Neutrophils/µL** **Lymphocytes/µL** **Glucose mmol/L** **(serum glucose mmol/L)** **Protein g/L** **CLAT**	 **40** **984** **0.5** **(4.6)** **1.94** **Positive**	**Positive**	**Chest radiograph not available**	**Not available**
Patient 10	**68**	**CSF:** **Neutrophils/µL** **Lymphocytes/µL** **Glucose mmol/L** **(serum glucose mmol/L)** **Protein g/L** **CLAT**	 **0** **44** **3.1** **(4.8)** **1.6** **Positive**	**Positive**	**Chest radiograph not available**	**Not available**

Table 3c: Investigations of patients with dual infection (Patients 11-15)

	CD4 T cells/µL	CSF		CSF TB CULTURE	Chest radiography	Neuroradiology findings
Patient 11	**Unknown**	**CSF:** **Neutrophils/µL** **Lymphocytes/µL** **Glucose mmol/L** **(serum glucose mmol/L)** **Protein g/L** **CLAT**	 **28** **12** **1.2** **(5.8)** **0.55** **Positive**	**Positive** **MDR TB**	**Chest radiograph showed consolidation in the right upper zone and reticular nodular shadowing in the left lower zone**	**Not available**
Patient 12	**218**	**CSF:** **Neutrophils/µL** **Lymphocytes/µL** **Glucose mmol/L** **(serum glucose mmol/L)** **Protein g/L** **CLAT**	 **0** **240** **0.8** **(7.3)** **3.83** **Positive**	**Positive**	**Chest radiograph showed reticular nodular infiltrates and hilar adenopathy**	**CT brain: prominent ventricular system, hypodensities in basal ganglia**
Patient 13	**53**	**CSF:** **Neutrophils/µL** **Lymphocytes/µL** **Glucose mmol/L** **(serum glucose mmol/L)** **Protein g/L** **CLAT**	 **0** **0** **2.7** **(6.1)** **0.41** **Positive**	**Positive**	**Chest radiograph normal**	**Not available**
Patient 14	**7**	**CSF:** **Neutrophils/µL** **Lymphocytes/µL** **Glucose mmol/L** **(serum glucose mmol/L)** **Protein g/L** **CLAT**	 **0** **0** **0.3** **(4.4)** **0.34** **Positive**	**Positive**	**Chest radiograph not available**	**Not available**
Patient 15	**218**	**CSF:** **Neutrophils/µL** **Lymphocytes/µL** **Glucose mmol/L** **(serum glucose mmol/L)** **Protein g/L** **CLAT**	 **40** **690** **1.3** **(4.6)** **Not available** **Positive**	**Positive** **MDR TB**	**Chest radiograph showed hilar adenopathy with nodular infiltrates**	**MRI spine normal,** **CT brain: hypodensities right parietal lobe**

TBM was diagnosed posthumously in 12 patients. 6 patients with co-infection were found to have multidrug-resistant TBM on culture, with one of them having extensively drug-resistant TBM (XDR TBM). The in-hospital mortality was 80% (12/15), with only three patients surviving to be discharged (Table 4).

Table 4: Outcomes of patients with dual infection

	TB treatment commenced	CCM treatment commenced	Patient outcome
Patient 1	Yes	Yes	Demised
Patient 2	Yes	Diagnosis made posthumously	Demised
Patient 3	Diagnosis made posthumously	Diagnosis made posthumously	Demised
Patient 4	Diagnosis made posthumously	Yes-demised on day 1 of treatment	Demised
Patient 5	Diagnosis made posthumously	Yes	Demised
Patient 6	Yes	Yes- Fluconazole only, patient refused Amphotericin B	Demised
Patient 7	Diagnosis made posthumously	Yes	Demised
Patient 8	Yes	Yes	Demised
Patient 9	Diagnosis made posthumously	Yes- demised after 7 days of treatment	Demised
Patient 10	Yes	Yes	Discharged well
Patient 11	Yes	Yes	Demised
Patient 12	Yes	Yes	Discharged well
Patient 13	Diagnosis made posthumously	Yes	Demised
Patient 14	Diagnosis made posthumously	Yes	Demised
Patient 15	Yes	Yes	Discharged well

Discussion

Patients with tuberculous meningitis (TBM) and cryptococcal meningitis (CCM) co-infection have been infrequently documented in the literature, with limited available data on its occurrence.[11,12,13] In our study comprising severely immunocompromised HIV-infected adults with TBM, 3.5% (5/15) were diagnosed with co-infection with TBM/CCM, a rate consistent with the existing literature.[11,12] Notably, Fang *et al*. (2017), reported a co-infection rate of 0.6% (23 cases of co-infection of 4053 total TBM cases) in China between 1993 and 2006.[11] Additionally, other studies have documented co-infection rates ranging from 2.7% to 3.8%.[12] The higher prevalence of co-infection observed in our population compared to more developed regions may be attributed to the high incidence of tuberculosis (TB) in South Africa.[4] Furthermore, a study conducted in Ethiopia by Jemal *et al*., 2021, examining the prevalence of cryptococcal antigenemia among HIV/AIDS patients found a prevalence of 11.43%, with a subset of TB-positive patients demonstrating rates of 43.8% and 31.2%, for pulmonary and extrapulmonary TB, respectively.[17] Although this study provides insights into the potential incidence of co-infection, it focused on extrapulmonary TB rather than specifically on TBM.

Analysis of the demographic characteristics of our study participants revealed an age range from 14 to 56 years, with a mean age of 37 years. These findings mirror those reported by Fang *et al*. (2017), whose investigation into TBM and CCM co-infection in Chinese patients revealed a mean age of 35.0±2.8 years (95% confidence intervals=29.3–40.7) at diagnosis of co-infection.[11]

In our cohort, the proportion of females among patients with dual infection exceeded that of males (9 females, 6 males), in contrast to previous findings on co-infection with CCM/TBM, which demonstrated a male predominance.[11,18] The small numbers in this study is acknowledged but this observed gender distribution may be attributed to the higher prevalence of HIV among females

(20%) compared to males (12%) in South Africa, a significant factor considering that the majority of our patients were HIV positive.[1]

Notably, our study revealed a similarity in the clinical presentation of CCM and TBM co-infection, characterised by symptoms such as headaches, fever, photophobia and altered consciousness levels, potentially contributing to diagnostic delays or missed diagnoses.[9,11,18] Further complicating the diagnostic process, similarities in cerebrospinal fluid (CSF) profiles between TBM and CCM were identified, although co-infected individuals tended to exhibit higher CSF protein and cell counts.[8] Specifically, among the patients with TBM and CCM co-infection in our cohort, the median CSF neutrophil count was 0/µL, lymphocyte count was 44/µL, glucose was 0.8 mmol/L, and protein was 0.83 g/L. These findings align with those reported by Ellis *et al*. (2018), in their case series from Uganda, where the baseline median CSF white cell count was 60 cells/µL (<5–2200 cells/µL) and median protein was 1 g/L(0.2–3.56 g/L).[13] Multivariate analysis conducted by Vidal *et al*. (2017), in patients with TBM infection alone showed CSF neutrophil predominance, pleocytosis and protein levels exceeding 1.0 g/L.[19] CSF microscopy, including Ziehl-Neelsen staining for acid-fast bacilli (AFB) in TBM cases, demonstrated limited diagnostic utility with AFB identified in only 5.5% of cases.[19] Moreover, while a high opening CSF pressure, low CSF white blood cell count and positive cryptococcal antigen latex agglutination test were indicative of CCM, they were not universally present.[19] India ink staining of CSF showed yeast compatible with *Cryptococcus* spp. in 84% (82/98) of cases.[19] A cryptococcal antigen latex agglutination test of CSF was positive in only 82% (80/98) of cases.[19] Collectively, our results underscore the challenge of relying solely on CSF studies to differentiate between CCM and TBM. Integration of clinical, radiological, and additional laboratory assessments is essential for accurate diagnosis and appropriate management of these dual infections.[19]

The diagnosis of co-infection poses significant challenges, particularly in cases of TBM, given its paucibacillary nature.[12] This study predates the introduction of advanced diagnostic modalities such as the Xpert® MTB/RIF Ultra and the lateral flow urine lipoarabinomannan (LF-LAM) assay, which have since augmented tuberculosis (TB) detection.[20] The Xpert® MTB/RIF assay, capable of real-time PCR detection of *M. tuberculosis* and rifampicin resistance has demonstrated potential in expediting TBM diagnosis.[12] Recognizing its value, the World Health Organization (WHO) advocates for its primary use in TBM diagnosis, reporting a sensitivity of approximately 60-70% and a specificity nearing 100%, thereby enhancing diagnostic timeliness.[21] Additionally, the LF-LAM assay, with a sensitivity of 45% and specificity of 92% in severely immunocompromised individuals holds promise as a point-of-care TB diagnostic tool, particularly endorsed for HIV-positive populations by the WHO.[20] While anticipating the introduction of superior diagnostic methodologies, such as Xpert® MTB/RIF to bolster microbiological confirmation of TBM, it is conceivable that the prevalence of TBM/CCM co-infection may rise.

In this study, the in-hospital mortality rate was noted to be 80% (12/15), with only three patients surviving for discharge. Ellis *et al*. (2018), reported a 60% in-hospital mortality rate in their cohort of patients with CCM/TBM co-infection.[13] Wong *et al*. (2012), found 62% of HIV-infected patients with *Mycobacterium* infection had multiple infectious causes of death at autopsy, including cryptococcosis.[10] Mortality from cryptococcal meningitis alone remains unacceptably high in sub-Saharan Africa.[22] The in-hospital mortality rate of CCM reported from a district hospital in the Eastern Cape, South Africa was around 30% whilst a study in a rural area in KwaZulu Natal reported around 40.5%.4 In contrast, assumed 3 month mortality rates of high-income regions such as Eastern and Central Europe and Oceania was only 9%.[22] The high early

mortality rate associated with CCM may also lead to an underdiagnosis of co-infection, as CCM patients may die before being diagnosed with TBM.

Another disconcerting finding was the number of multi-drug resistant TBM cases observed in our study. Six patients with co-infection were found to have multidrug-resistant TBM on culture, with one having extensively drug-resistant TBM (XDR TBM). Heemskerk *et al*. (2017), described the clinical outcome of patients with drug-resistant TBM which had a high mortality rate, with eleven of 16 (68.8%) of those with MDR TB dying by nine months.[23] The majority of patients with MDR TBM died by day 27 despite having initiated treatment.[23] Hence it can be postulated that dual infection would lead to much poorer patient outcomes with higher mortality, as was evident in this case series. The expeditious initiation of treatment significantly ameliorates the prognosis of both TBM and CCM. However, prolonged drug regimens expose patients to diverse drug toxicities, further complicating morbidity and mortality in cases of dual infection.[23]

Despite a growing understanding of the local host immune response in each individual infection, there is a lack of information regarding the immunology in co-infections.[8] Both *C. neoformans* (or cryptococcus) and *M. tuberculosis*, being intracellular pathogens, can activate a type I immune response that is characterised by the interplay between adaptive immune response cells and innate immune cells e.g., macrophages and dendritic cells.[8] HIV reduces the quantity and capability of all immune cells, causing weakened immune responses and an increased likelihood of developing disseminated tuberculosis and cryptococcosis.[8]

Although the epidemiology, immune responses and major impact on HIV-related mortality of TB and cryptococcosis overlap, the co-infection of the two is not well documented.[14,24] The low sensitivity and specificity of the available TB diagnostic tests for those with advanced HIV may be the cause of missed cases of TBM.[24] Using sensitive and specific TB diagnostics for systematic screening of patients who are severely immunosuppressed with HIV will likely increase the number of microbiologically confirmed cases of TB co-infection, and could result in an increase in the number of hospitalised HIV patients with confirmed TB diagnosis.

Limitations

The findings of our study necessitate cautious interpretation, recognizing the inherent challenges in diagnosing extrapulmonary or disseminated tuberculosis. In the current study, initially microbiologically confirmed cases of TB meningitis were identified, and were then evaluated for cryptococcal meningitis co-infection. Conversely, all laboratory-confirmed cases of CCM could have been assessed for microbiologically confirmed evidence of TB co-infection. This approach could have enhanced diagnostic sensitivity, which we acknowledge as a limitation in this study.

The absence of specific TB diagnostics for such cases is likely to have introduced a bias towards underdiagnosis. Our study solely focused on patients meeting the criteria for “definite” tuberculous meningitis (TBM) as outlined by the consensus clinical case definition proposed by Marais *et al*. (2010).[25] Patients categorized as "probable" or "possible" TBM were excluded from our study, and this could have resulted in some patients with TBM being missed.[25] Given the retrospective nature of this case series, incomplete medical records and data gaps may also have impacted our analysis. The limited number of patients included in this series reflects the inherent difficulty in diagnosing co-infection of TBM and CCM. Moreover, not all specimens may have been sent for TB culture, potentially leading to missed diagnoses.

Conclusion

In this study, we found that dual infection of the meninges with *M. tuberculosis* and *C. neoformans* in HIV-infected patients is rare. However, the diagnosis may often be missed and therefore under-reported. The underdiagnosis of dual infection may result in patients not being treated appropriately and adequately.

This case series highlights the difficulty of diagnosing TBM-CCM co-infection. This study was conducted prior to the introduction of the Xpert® MTB/RIF Ultra test as well as the lateral flow urine lipoarabinomannan assay. We postulate that with the subsequent introduction of these tests, the diagnosis of TBM may improve with earlier detection and better yield. Co-infection reflects the advanced immunosuppression characteristic of patients with HIV-associated CCM, and the complexities of diagnosis and management in patients at risk of intercurrent opportunistic infections. Our research demonstrates the need to consider co-infection at baseline diagnosis, as well as the need to remain vigilant for co-infection throughout the follow-up period.

Declarations

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Ethics statement: The proposal was submitted to the Biomedical Research Ethics Committee (BREC) of the University of Kwa Zulu Natal and the Kwa Zulu Natal Department of Health for evaluation and approval. The ethics approval number for this study is BREC/00005669/2023. The data was analyzed anonymously to ensure the privacy and confidentiality of the participants.
Authors' contributions: All authors contributed to the final manuscript. FM conducted the literature review, data collection as well as assisted in the manuscript write-up. MM assisted with the study design and data analysis and ZM assisted with analysis and manuscript review.
Data availability: The data supporting this study's findings are available from the corresponding author, FM, upon reasonable request.
Disclaimer: The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy of the affiliated institutions of the authors.

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