Tuberculomas Meningitis in Patients Living with HIV

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Abstract

Background: Tuberculosis Meningitis (TBM) is a devastating manifestation of tuberculosis (TB) caused by the hematogenous spread of Mycobacterium tuberculosis. TBM is particularly severe in HIV infected patients. In Morocco, TB and HIV are the main public health problems; the rate of TBM has not been well defined. The objective of this study was to describe the presentation and outcome of TBM during HIV infection in our department.

Patients and Methods: This was a retrospective study of cases of TBM among HIV infected persons presenting to a unit of infectiology of UHC Ibn Rochd of Casablanca between 2010 and 2015. The diagnosis of TBM was made with clinical, laboratory and radiological features.

Results: During the study period, 1.43% (50/3496) of HIV-infected patients had TBM with a small female dominance. Mean age was 34 years with a range of (21-58). TBM revealed the HIV infection in 46 cases (92%). The most common clinical manifestations were headache and fever. Median CD4 cell count was 134 cells/mm³. Lymphocytic meningitis was frequent with bacteriological confirmation in 20% of the cases. Brain CT revealed tuberculomas in 40% cases. All patients received anti-tuberculous and 70% received adjunctive steroid therapy. However, 34% of patients died within the first year.

Conclusion: TBM is a frequent circumstance revealing HIV infection in our context. It remains a common cause of mortality of HIV infected patients. Mortality was correlated with neurological disorders and profound immune suppression. Early diagnosis and prompt treatment are critical to successful outcomes.

Keywords: Tuberculosis Meningitis; Cerebrospinal Fluid; Tuberculoma; HIV infection

Introduction

Tuberculosis (TB) remains a major public health problem in Morocco and represents the most frequent AIDS-defining opportunistic infection [1]. The annual incidence of TB in Morocco was estimated at 83/100,000 people per year of the adult population and the prevalence of HIV infection among TB patients is 1.7% [2]. HIV intensively increases the risk of tuberculosis meningitis (TBM) because there is an augmented susceptibility for reactivation and dissemination of TB in these patients [3,4].

TBM is one of the most severe and lethal complications of TB [5]. TBM is caused by the hematogenous spread of the bacilli, from pulmonary TB or from the rupture of subependymal tubercle into the subarachnoid space [6,7]. However, the mechanism by which the bacilli invade the blood-brain barrier and the exact trigger of discharge into the subarachnoid space is not fully understood [6]. TBM diagnosis and treatment are complicated by variable cerebrospinal fluid (CSF), drug interactions and proper timing of antiretroviral therapy (ART) initiation after starting TBM treatment given the possibility of immune reconstitution inflammatory syndrome (IRIS) [3]. IRIS develops in 9-47% of persons with HIV infection and TBM who start ART and is associated with a mortality rate of 13% - 75% [8]. Patients living with HIV have an increased risk of poor clinical outcomes with mortality rates as high as 67% against 25% in HIV uninfected patients [7]. In Morocco, in spite of the high burdens of HIV and TB, studies concerning TBM and HIV are rare. Furthermore, despite the availability of TB and HIV, the prior majority of HIV-infected patients with TBM still present with severe immunosuppression. This study was designed to outline the characteristics of TBM patients in our unit.

Patients and Methods

This was a retrospective study of HIV infected patients admitted with TBM at the University Hospital Center (UHCh) of Casablanca, from January 2010 to May 2015. The diagnosis was recognized using clinical symptoms, CSF analysis and radiological features. All patients had macroscopic examination, protein, glucose quantification, cell count, Ziehl-Neelsen (ZN) staining and Mycobacterium tuberculosis culture on environment Lowenstein completed on CSF. Additionally, some patients had TB polymerase chain reaction (PCR) tests (real time PCR, 2720 thermal technology, applied biosystem by life technology, USA), spherulys serology, India ink staining and/or Cryptococcus Lateral Antigen Testing (Pastorex crypto plus, Biord, France) completed on CSF as indicated. Brain CT was completed in most cases to exclude obvious mass effect prior to lumbar puncture and MRI of the brain was completed as indicated, often to look for evidence of tuberculoma. Tuberculomas was identified as a low or high density round/ lobulated mass with irregular walls showing ring enhancement post contrast. Chest X-ray and sputum samples were collected to look for evidence of pulmonary TB, when indicated abdominal ultrasound and histopathologic examinations were collected when pertinent to look for evidence of pulmonary TB.

CSF finding consistent with TBM include high protein, low glucose and a high mononuclear to polymonuclear leucocyte ratio. TBM is also suspected if patient has meningeal involvement with features suspicious of extrameningeval TB. TBM is confirmed by culture or molecular confirmed (PCR) Mycobacterium tuberculosis in CSF.

Patients were treated with standardized TB treatment; including isoniazid, rifampicin, pyrazinamide, and ethambutol for two months, followed by rifampicin and isoniazid for at least four months. Total duration varied from six to nine months. ART was advised for all patients. The first line was tenofovir, entecitabine, efavirenz, nevirapine.

Data was collected from medical records and analyzed using Excel support and SPSS 16.0. Univariate analysis was executed to identify variables associated with inpatient mortality during hospitalization. Statistical method was CH2 and p-value < 0.05 was considered statistically significant.

Results

During the study period, 130 cases of meningitis in patients living with HIV were observed. The most frequent cause was TBM 39% (50/130) and cryptococcal meningitis 33% (43/130). The prevalence of TBM among all HIV patients was 1.43%. Of these 50 cases, 96% originated from Morocco and two patients were from Mali. A slight majority of patients were female (n = 27, 54%), overall mean age was 34...
years with a range from 21-58 years. Patient demographics are shown in Table 1. Most patients (90%) had heterosexual intercourse. Majority of patients were from low socio-economic backgrounds (80%). Sixty (33%) cases have a history of previous TB and seven (14%) patients had TB contact positive. 12/50 (24%) of patients were receiving TB treatment at time of TBM for a median duration of 24 days. The symptoms evolved for two weeks or more before admission (97%). Majority of patients have a general signs of TB infection (night sweat seen in 80%, weight loss in 76%). Pulmonary symptoms were rarely presenting the symptoms (30%) of cases. The most common clinical manifestations were headache (68%) and fever (46%). Typical meningal syndrome was observed in only 17 (34%) patients. Neurological symptoms noted on admission were unconsciousness (34%), motor deficiency (30%) and convulsions (10%). We summarized clinical presentation in Table 1. Most patients underwent brain CT (n = 45/50, 90%) with a minority (n = 12/50, 24%) having undergone brain MRI with gadolinium. While the majority (n = 26/45, 58%) were normal, a tuberculoma was seen in 19 (42%) cases. Five (10%) patients demonstrated hydrocephalus and cerebral infarct respectively as shown in figures 1 and 2. CSF examinations are summarized in Table 1, 80% of cases showed a lymphocytic pleocytosis. The median protein level was 0.83 mg/dL (IQR: 0.2-3.09), median glucose level was 0.4 mg/dL (IQR: 0.18-1.38) and median white cell count (WCC) of 108 cells/ml (IQR: 0-700). A protein level was more than 0.4 mg/dL in 30 (60%), a glucose concentration was less or equal to 0.45 mg/dL in 17 (34%) cases. No Acid fast bacilli (AFB) smears were positive. Mycobacterium tuberculosis was cultured from 10/50 (20%) of CSF samples. PCR was positive in three cases (n: 3/11, 27%); no patient was found to have with multidrug resistant TB.

Twenty five (50%) patients had extra-meningeal TB. Chest radiograph was consistent with TB in 23 (46%) cases. The most frequent pulmonary lesions were infiltrates (57%) and cavity (26%) of abnormal Chest X-ray. Four (17%) patients presented with miliary TB. Seven (14%) patients had confirmed pulmonary TB. Abdominal ultrasound showed features of abdominal TB in seven patients. The median CD4 count was 90 cells/µL (IQR = 39-137). The majority of patients (82%) had CD4 count less than 200 cell/mm³. HIV diagnosis was concomitant to a diagnosis of TB in 92% of cases. Only four patients (8%) were receiving ART at the time of hospital admission. Anti-tuberculous treatment was started immediately after clinical suspicion and followed for 9 to 12 months. Adjunctive steroid therapy was initiated at a dose of 1.5 mg/kg/day in 70% of patients during the first month and gradually reduced during the second month. Nine (18%) patients developed reversible side effects; five with isoniazid and four with rifampicin. Four patients (8%) needed placement of a ventriculoperitoneal shunt for hydrocephalus. Three (6%) patients developed IRIS with a median of time onset of three to six months. Thirty three (66%) patients recovered after antituberculous treatment and stayed well at 12 months of follow up. Three patients (6%) have residual disability associated with adverse effects of medication. Inpatient mortality was 34% for an average of ten days after admission. We didn't found the significant variables associated with mortality (Table 2).

Discussion

The increased incidence of HIV infection has led to the resurgence of TB in Morocco. Neurological TB, occurs in 5 to 8% in HIV infected patients; five times more frequent than in patients without HIV [6,9]. TBM accounts for approximately 1% of all cases of TB [5]. This study founded that the prevalence of TBM in HIV infected patient at the UHC of Casablanca was 1.43%. This result was lower than that of studies conducted in Cameroon (8%) and India (7%) [3]. TBM occurs most often in persons over 45 years, frequently appearing as a reactivation of...
a latent infection [10]. In our study, the most affected age group was between 21-40 years, 80% of cases. This could be explained by the young age of our population and the high incidence of TB in our region. A slight female predominance was observed, this could be explained by the feminization of HIV in Morocco. The prevalence of CNS-TB infections in females have been described in other studies from industrialized countries and suggest a gender related difference in the pathogenesis of TB [11]. The typical clinical picture of meningitis is rarely found. Indeed, the range of signs is wide and the onset of symptoms may be insidious or abrupt [7]. Usually, HIV infection does not modify the presentation of TBM [12], however, during HIV infection, the diagnosis of TB is complicated by the possibility of opportunistic intracranial infections and malignancies [3]. Typical meningeal stiffness was observed in only 34% of our patients, and the most frequent clinical symptoms were headache (68%) and fever (46%), similar to those of other studies [7,13]. Headache was present in 75% in other studies [6,14,15]. This difference could be explained by lower CD4 count of our patients and patients more severely immune depresses will present unusually [16]. However, our study was distinguished by the frequency of unconsciousness noted in 38% of cases. More so, TB have an insidious onset with variable duration of symptoms from a few days to many months [7]. The gradual onset of symptoms before the hospitalization noted in 84% of cases in our study is consistent with that of Luma et al [7]. Atypical CSF result are more common in HIV infected patients, including lower CSF protein, higher glucose levels, lower CSF WCC and even completely normal CSF finding have been reported in 25% to 33% of HIV infected TB cases [16-22]. The absence of CSF pleocytosis occur generally in patients with low numbers of lymphocytes in the peripheral blood (CD4 T-cell counts < 50 cells/MI), which may be reflected by a low lymphocytes count in the CSF [7,21]. We found that the median WCC was much higher than in other studies [7,23]. The demonstration of Mycobacterium tuberculosis in CSF is the gold standard for diagnosis; and for drug-susceptibility testing. Though, CSF MT culture is slow and insufficiently sensitive (roughly 60-70%) [3,6,24,25]. This fact could be illustrated in our study where confirmatory diagnosis by culture was in only 20% of patients. The number of positive results in this study was lower than that in a previous study [6]. This finding may be related to the low CSF volume used for culture examination [6]. Thus, CSF microscopy with Ziehl-Neelsen staining for AFB (acid fast bacilli) is the test used most often worldwide for TB diagnosis, but has poor sensitivity (10-20%) in TBM and cannot be relied upon to rule out TB [3,13,26-27]. However, the sensitivity can be improved by increasing the CSF sample volume to 6 ml and shortening the time for examination of the slide [6,7]. In this study, in any case CSF microscopy was positive. Other study had also low finding rates [7]. Nucleic and amplification (NAA) tests on CSF have better sensitivity and specificity compared with microscopy and culture and it can speed the diagnosis of tuberculosis from several weeks to 2 days [3,9]. In our study, PCR did not improve the yield because Mycobacterium tuberculosis was detected in only 2 smears from positive patients. Indeed, in our study, it has been performed in 10 of the cases reported here; where microbiological research in the CSF remained negative. It was positive in two cases and this result was negative with culture positivity in one case. The poor sensitivity of NAA in CSF has been reported before [13]. For radiographic assessment of TBM, MRI better characterizes the typical finding of TBM. However, in our unity, CT scan is a common practice in CNS disease investigation. The typical finding of TBM including brainstem involvement, leptomeningeal enhancement, vascular and cranial nerve involvement [28-30]. However, these radiographic finding are not specific to TBM, and may not be sufficient to exclude other CNS co-infections [3]. An increased rate of tuberculosis in patients co-infected HIV-TB versus HIV uninfected patients is reported [3,13]. In our study, tuberculosis was seen in 38% of cases, this finding is similar to that seen in one study from India (39%) [31] and lower than what was reported in other study (45%) [6]. CSF infarctions and communicating hydrocephalus are also reported in TBM [32]. They were present in only 10% of cases respectively [13]. They were seen on CT scans in 12% and 28% respectively of adults with TB in other study [33,34]. The presence of extrameningeal TB should be searched for any case of TBM using microscopy and mycobacterial culture of appropriate extrameningeal specimens including sputum [3]. Chest x-ray finding were abnormal in 46% of our cases and seven patients becoming culture positive. This shows the importance of not trusting on chest-x ray and sputum to support the diagnosis of TBM [9, 13]. HIV infection is recognized as the most common risk factor associated with TB and TBM may be the initial presentation of HIV infection, as was perceived in 92% of our patients [35, 36]. Consequently, HIV status should be defined if TBM is recognized [9]. Furthermore, sever immunosuppression, increases the odds of having TBM [36,37]. Leeks and al were reported that HIV infected patients with extrapulmonary TB and CD4 less than 100 were more likely to have TB [4]. Other studies also founded that declining CD4 lymphocytes count can be associated with increasingly severe form of TB including TBM, but this remained understudied [36,38]. This is consistent with our results when most of the patients had severe immunosuppression. Previous studies also reported results of severe immune suppression with median CD4 count reaching sixteen to twenty in other study conducted in Cameroon. Study conducted by Kingkaew et al, which founded that 71, 8% of HIV infected patients with TBM had CD4 lymphocyte counts < 100 [40]. Anti-TB treatment should be started once TB is suspected because of the associated high case fatality [3,7]. In Morocco, the TBM treatment regimens are standardized and comply with international recommendations including those of the WHO and international Union against Tuberculosis and Lung Disease [41]. All the French and American learned societies recommend the use of corticosteroids in addition to TB treatment, although the results of literature are not all consistent [42-44]. In a study of 270 patients, the use of corticosteroids does not find a significant improvement in survival adult patients with TBM [45]. Another study about 545 patients showed that the adjuction of dexamethasone to the anti-TB regimen reduced mortality but did not prevent disability in survivors [46]. TBM is the most lethal form of TB especially in HIV infected patients severely immune depressed [47]. Its mortality rates are considerably increased by HIV infection, with 9 months survival rates less than 40% in HIV infected patients, compared with more than 70% in HIV uninfected patients [3]. 34% of our patients died, this case fatality is lower to that founded in other study (79%) [23]. Higher rates of mortality have been described in other study conducted in Cameroon. Study conducted by Al- Shafy et al, which founded in other study (79%) [23]. Higher rates of mortality have been described in other study conducted in Cameroon. Studies from Brazil and China reported rates of mortality at 29% [40]. In HIV infected patients, a lower CD4 cell counts [3,23], focal signs and altered consciousness on admission, were found to be a factor associated with poor prognosis [47]. Previous study found also an association between immune suppression, neurological deterioration at admission and poor prognosis in HIV infected TB patients [6,48,49]. Some studies reported other factors associated with death including disease duration of more than 14 days, drug resistance TB and low serum sodium concentration [23,49]. EL Sahly et al. founded that older patients were more likely to die within 180 days of diagnosis than younger patients [50]. TB- IRIS is a severe complication, in HIV infected patients receiving TB treatment. It occurs usually approximately 2 weeks after ART start after the introduction of ART (30%) [6]. TB-IRIS is characterized by high CSF neutrophil count and Mycobacterium tuberculosis culture positivity [49]. Cases of expanding tuberculosis and abscesses have been described in paradoxic TB-IRIS [3]. The treatment is not finally established, it based to corticosteroids, often needing extension months into TB treatment [3]. TB-IRIS has been reported in twenty to forty percent of patients receiving anti-TB therapy for TB in other studies conducted in South Africa [49,51]. There were limitations in our study. Its retrospective nature, the small sample size and the study concerned only one referral hospital does not capture the real picture of the burden of TBM among HIV-infected patients in...
Morocco. However, the study represents some informations which can help a clinician’s in diagnosis and management of TBM in HIV especially in a setting with limited resources. With these challenges, we have conducted a prospective study with the aim of heaving more light on the burden of TBM both in HIV-infected and HIV-uninfected patients.

**Conclusion**

The eminent results to extract from our study are that TBM may be the initial presentation of HIV infection; clinical presentation and lab exam are often atypical. Physician should do a LP in the presence of any warning sign of meningitis. We have also found that TBM has a high rate of mortality in PLWH and advanced stage of HIV and the presence of neurological symptoms at admission are correlated with high rate of mortality. Starting early TB treatment may decrease the mortality rate by increasing the CD4 count.

**References**

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