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Tuberculous Meningitis in HIV-Infected Individuals

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Abstract

HIV-infected individuals are at increased risk for all forms of extrapulmonary tuberculosis, including tuberculous meningitis. This risk is increased at more advanced levels of immunosuppression. The time interval between onset of symptoms and presentation to medical care may vary widely, and consequently individuals may present with acute or chronic meningitis. The clinical presentation of tuberculous meningitis in HIV-infected individuals is more likely to include an altered level of consciousness, cranial imaging is more likely to show cerebral infarctions, and the yield of culture of cerebrospinal fluid may also be greater. Given that delayed initiation of therapy is a strong predictor of mortality in cases of tuberculous meningitis, clinicians must consider tuberculosis in the differential diagnosis of the HIV-infected individual with acute or chronic lymphocytic meningitis. Additional treatment considerations for HIV-infected individuals include the timing of initiation of antiretroviral therapy, the potential for drug–drug interactions, and the role of adjunctive corticosteroid therapy.

Introduction

Meningitis is the most devastating manifestation of tuberculosis. In a recent case series from the United States, 17% of patients with tuberculous meningitis (TBM) died during the first 9 months of therapy [1•]. In countries with a high incidence of tuberculosis, the mortality rate may be greater than 50% [2], and survivors may be left with significant neurologic disabilities. In this review, we discuss the influence of HIV infection on the pathogenesis and clinical course of TBM, and review therapeutic considerations for the HIV-infected individual with TBM.

Pathogenesis of TBM

Overview

Tuberculosis of the central nervous system (CNS) may present as meningitis, tuberculous granulomas (tuberculomas), or tuberculous brain abscess, and these processes may occur as isolated disease or as part of disseminated (miliary) tuberculosis. Limitations of animal models have hindered efforts to describe the exact sequence of events that leads to the development of TBM [3••].

Like all forms of tuberculosis, infection is acquired by the inhalation of bacilli within droplet nuclei, followed by early hematogenous dissemination. A critical step in the development of TBM is the deposition of mycobacteria adjacent to the subarachnoid space or ventricles during this dissemination. With adequate host immune response, caseating or noncaseating

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granulomas will form at sites of dissemination. These tuberculomas may remain clinically silent or may present as intracranial space-occupying lesions [3••]. Post-mortem studies of individuals who died of pulmonary tuberculosis, without evidence of CNS tuberculosis, have found that a significant proportion of individuals had tuberculomas in the CNS (brain, meninges, or choroids plexus), indicating that seeding of the CNS often occurs in pulmonary tuberculosis [4].

In autopsy studies of individuals who had died of TBM, Rich and McCordock [5] found evidence that, in almost all cases, a subependymal or subpial tuberculoma ("Rich focus") had ruptured into the subarachnoid space. They postulated that this rupture was the event that precipitated the development of TBM. Subsequently, Donald et al. [6] argued that miliary tuberculosis shares this same pathogenic mechanism, with the more widespread dissemination of miliary disease increasing the likelihood of formation of a tuberculoma at a cortical or meningeal site.

Rupture of a Rich focus into the cerebrospinal fluid (CSF) induces an immune response and leads to the formation of a tuberculous exudate surrounding the brainstem and cerebellum. This exudate is composed of neutrophils, mononuclear cells, erythrocytes, and variable numbers of bacilli. Communicating hydrocephalus may develop as a consequence of decreased CSF reabsorption in the presence of the inflammatory exudate. Accumulation of tuberculous exudate may also interrupt CSF flow through the ventricles, leading to obstructive hydrocephalus. The hydrocephalus of TBM is more commonly seen in children, and is more progressive than the transient hydrocephalus that may accompany bacterial meningitis. The immune response may trigger a vasculitis within the vessels of the circle of Willis, the vertebrobasilar system, and branches of the middle cerebral artery, leading to infarction in the areas that are supplied by these vessels. Cranial nerve impairment may develop as a consequence of these infarctions, or from direct compression by the tuberculous exudate [3••].

Influence of HIV infection on the pathogenesis of TBM

Infection with HIV is associated with increased risk of activation of latent infection, as well as increased risk of rapid progression of primary infection, without an intervening period of latency. Without HIV infection, individuals with latent infection have a lifetime risk of developing tuberculosis that ranges between 10% and 20% [7]. In contrast, the HIV-infected individual will carry a 10% annual risk of progression to active infection, with increasing risk as the CD4+ count declines [8]. The use of antiretroviral therapy (ART) reduces this risk, but this reduction may be tempered by incomplete immune restoration of tuberculosis-specific lymphocytes, poor adherence, or treatment interruptions related to drug availability.

Patients with HIV and active tuberculosis have an increased risk of extrapulmonary tuberculosis, and this risk will also increase with declining CD4+ count [9]. Post-mortem examinations have commonly found disseminated tuberculosis among HIV-infected individuals from high-incidence countries. In an autopsy study from Kenya, disseminated tuberculosis was found in 41% of HIV-infected patients, compared with only 6% of HIV-uninfected patients [10].

This increased risk of extrapulmonary disease leads to an increased risk of meningitis. Among culture-proven cases of tuberculosis in Spain, 455 HIV-infected patients were compared with 1750 HIV-uninfected patients. CSF was the site of culture for *Mycobacterium tuberculosis* in 2% of the cases in patients without HIV infection, compared with 10% of patients with HIV infection [11]. The association between HIV and TBM may be stronger in patients with a history of intravenous drug use [12]. As a consequence of the overlapping HIV and tuberculosis epidemics, in some populations tuberculosis has become

the dominant cause of meningitis, more common than acute bacterial infections such as *Neisseria meningitidis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae* [13].

Clinical Course

The duration of symptoms of TBM prior to presentation has been reported to vary from 1 day to 6 months, and consequently may present as either acute or chronic meningitis. The nonspecific prodrome of TBM includes fatigue, malaise, anorexia, vomiting, fever, and headache; fluctuation of symptoms during this period is common. Acute presentations may be indistinguishable from bacterial meningitis. Occasionally, TBM may present as a progressive dementia, with social withdrawal and personality changes [14]. Active pulmonary tuberculosis accompanies TBM in 30% to 60% of cases [15,16].

Cranial nerve palsies may be seen on presentation, most commonly involving the sixth nerve, but the second, third, fourth, and eighth nerves may also be involved. Seizures may occur at any point during the initial illness or during the treatment period. Cerebral edema or brainstem infarctions may lead to pyramidal or cerebellar signs, and are associated with a depressed level of consciousness. The end-stage illness is characterized by deep coma, along with spasticity and posturing [17].

Analysis of CSF plays a central role in the diagnosis of TBM. Typically, there is a lymphocytic pleocytosis, with an elevated protein and low glucose levels [3••,18,19]. Diagnostic rules using clinical and CSF findings have been developed and tested in different populations, but the application of these rules beyond their source populations is uncertain. In addition, diagnostic rules have not been developed that can adequately distinguish between cryptococcal and TBM [18]. The classic neuroradiologic findings in TBM include basal meningeal enhancement, hydrocephalus, and infarctions in the supratentorial brain parenchyma and brainstem [20].

Risk factors for mortality

Stage at presentation—In the clinical staging system developed by the British Medical Research Council, patients meet criteria for grade 1 disease if they are alert and oriented without a neurologic deficit. Patients with grade 2 disease have a focal neurologic sign, or a Glasgow Coma Score from 10 to 14 (with or without neurologic deficit). In grade 3 disease, patients have a score less than 10.

Risk of mortality is highly correlated with the clinical stage at presentation. Patients who present with grade 1 are likely to survive, whereas patients with grade 3 disease have a high risk of mortality [21]. Additionally, the development of hydrocephalus, either on initial presentation or during the course of hospitalization, is predictive of mortality [22]. In these cases, the optimal treatment modality (osmotic agents, diuretics, external drainage, or ventriculoperitoneal shunts) has not been determined, and clinical decisions may depend on the resources of the treating hospital [18].

Diagnostic delay—Diagnostic delays of TBM are also associated with increased risk of mortality. In a study of 79 pediatric cases of TBM in Canada, a time interval between presentation and initiation of anti-tuberculous therapy of 3 days was associated with an increased risk of death [23]. In a similar study of 48 adults with TBM in France, a delay of 3 days between presentation and initiation of anti-tuberculous therapy was also associated with increased risk of death [15].

HIV—Several observational studies have compared TBM mortality rates of HIV-infected and -uninfected patients. In South Africa, eight of 34 children co-infected with HIV died

during treatment for TBM, while all 55 children without HIV survived [24]. Among adults in India, mortality at 6 months was also greater in the HIV-infected group (36% vs 10%) [25], and HIV-infected adults in Vietnam were at increased risk for morality at 9 months [26]. In each of these studies, the authors noted that ART was not available for the HIV-infected group.

In contrast, studies of adults in Los Angeles [27], Texas [1•,28], South Africa [29,30], and a study of children in India [31] did not find a mortality difference between HIV-infected and -uninfected individuals. It is not reported in these studies what proportion of HIV-infected individuals received ART. Among HIV-infected adults in Argentina, risk factors for death during hospitalization for TBM included a CD4+ count less than 50, and the presence of neurologic signs on admission [32].

Influence of HIV on the Clinical Presentation of TBM

Signs and symptoms

Several observational studies comparing the clinical presentation of TBM in patients with and without HIV infection have found that presenting symptoms such as fever, headache, vomiting, and weight loss are similar in both groups [11,24,25,27–31,33,34]. On examination, HIV-infected patients may be more likely to have lymphadenopathy [11,15,34] and hepatosplenomegaly [24].

An altered level of consciousness may be more prominent in HIV-infected individuals. Among patients with TBM in India, impaired cognition was exclusively seen in HIV-infected patients [25]. Similarly, a review of TBM cases in Texas found that HIV-infected patients were more likely to present with an altered level of consciousness [1•]. In contrast, studies of adults in Vietnam [30] and Spain [11] found no difference in rates of alerted mental status on presentation. In South Africa, HIV-uninfected children were more likely to have impaired consciousness on initial presentation [24].

Laboratory features

CSF findings—A number of studies have found no difference in the CSF parameters (cell count, protein, and glucose) of HIV-infected and -uninfected patients [1•,15,24,27,28,30,34]. Other studies, however, have found a lower CSF leukocyte count [25,35] and a lower protein level [25] in HIV-infected patients, and a higher opening pressure in HIV-uninfected patients [27].

There is wide variation in reporting of the sensitivity of CSF smear and culture in cases of TBM [36]. Likelihood of a positive culture may be improved by several technical factors, including the volume of CSF cultured (at least 6 mL) and direct examination of the smear for a minimum of 30 minutes [36]. CSF cultures yield *M. tuberculosis* more frequently in HIV-infected individuals with TBM [1•,37], perhaps due to greater mycobacterial dissemination within the CNS [25].

Serum findings—HIV-infected patients in Vietnam were more likely to have elevated liver transaminases, although the authors note that these findings may be a consequence of the epidemiology of HIV infection in the study population, with HIV infection strongly associated with intravenous drug use and viral hepatitis [34]. Similarly, an association between liver comorbidities and HIV was seen among cases of TBM in Texas [1•]. Anemia [24,25,31] and hyponatremia [33] were also more common in HIV-associated cases of TBM.

Radiographic features

Chest radiography—A study of TBM in South African adults found an association between HIV infection and radiographic evidence of concurrent pulmonary tuberculosis [29]. HIV-infected children in South Africa were more likely than HIV-uninfected children to present with hilar lymphadenopathy, pleural effusion, and cavity formation [24]. In contrast, other observational studies have not found an increased risk for extrameningeal disease in HIV-infected patients [1•,27,28,30,31].

Head CT—The influence of HIV infection on intracranial imaging studies has been examined in several studies. Meningeal enhancement was more common in HIV-infected individuals [11,24,25]. HIV-infected individuals were also more likely to present with cerebral infarcts [30] and mass lesions [15,24,27], and less likely to present with obstructive hydrocephalus [24,25].

These differences in intracranial imaging studies are reflected in a single study that compared the neuropathology of TBM in seven HIV-infected patients (not receiving ART) with the neuropathology of two HIV-uninfected patients. Tuberculous exudates in the HIV-uninfected patients were thick and gelatinous, covering the major vessels and obstructing CSF outflow, while in the HIV-infected patients, exudates were minimal and serous. Finally, infarctions were more commonly located in the basal ganglia in HIV-uninfected patients, and in the brain parenchyma in HIV-infected patients [25].

Treatment of TBM in the HIV-Infected Individual

Anti-tuberculous therapy

Overview—Pharmacokinetic studies suggest that isoniazid plays a central role in the treatment of TBM. For the anti-tuberculous agents, penetration into CSF has been shown to depend on the degree of protein binding in serum and the rate of renal clearance. Isoniazid achieves CSF levels that approach serum levels, both in the setting of inflamed and noninflamed meninges. Pyrazinamide also achieves high CSF concentrations, but the role of bacteristatic agents in the treatment of TBM is not well defined. Ethambutol and rifampin are moderately protein bound in serum and poorly penetrate CSF; levels may not rise significantly above the minimum bactericidal concentration of a susceptible strain [38].

Treatment regimens for TBM have been extrapolated from clinical trials for pulmonary tuberculosis. Guidelines from the joint committee of the American Thoracic Society, Infectious Disease Society of America, and the US Centers for Disease Control and Prevention (CDC) recommend initial four-drug therapy with isoniazid, rifampin, ethambutol, and pyrazinamide. After the first 2 months of therapy (the induction phase), pyrazinamide may be discontinued, and ethambutol may be discontinued once the strain is known to be susceptible to isoniazid. Although some investigators have found that 6 months of therapy may be adequate for the treatment of TBM [39], CDC guidelines recommend that treatment continue for at least 9 to 12 months [40]. Important considerations for the HIV-infected patient with TBM include the choice of rifamycin, timing of initiation of ART, and the use of adjunctive corticosteroids.

Choice of rifamycin

Interactions between anti-tuberculous therapy and ART: The use of a rifamycin agent is essential for successful short-course chemotherapy, and the failure to use a rifamycin has been associated with higher mortality in HIV-infected patients [41]. The choice of rifamycin should be influenced by considerations of interactions with ART. Rifampin has significant interactions with antiretroviral agents, due to its inductive effects on drug metabolism

through cytochrome P450 (CYP) 3A. The inductive activity of rifampin will lead to severely reduced levels of protease inhibitors and nevirapine. For this reason, when rifampin-based anti-tuberculous therapy is used in resource-limited settings, the CDC recommends the use of efavirenz-based ART. It is unknown whether dose adjustment of efavirenz is required [40], although most clinicians in the developing world maintain the daily dose of efavirenz (600 mg daily), with some reports suggesting appropriate efficacy.

Rifabutin is a rifamycin with significantly less induction of P450 enzymes. Consequently, rifabutin has less effect on the serum concentrations of antiretroviral agents. However, some of these agents will lead to changes in the metabolism of rifabutin. Concentrations of rifabutin will be increased with co-administrations of p450 inhibitors (such as ritonavir), and reduced with co-administration of p450 inducers (such as efavirenz). Clinicians should refer to frequently updated recommendations for the dose adjustments of anti-tuberculous drugs and ART. Although case reports have described the successful use of rifabutin in the treatment of tuberculosis of the CNS, more clinical research is needed to determine the optimal dosing of anti-tuberculous therapy and ART for the co-infected patient, particularly in the setting of TBM [42•].

Risk of acquired resistance: Risk of developing resistance on anti-tuberculous therapy is proportional to the bacillary burden, with cavitary pulmonary disease carrying the highest risk. Although the bacillary population within the CSF in cases of TBM may be comparatively smaller, given the association of HIV infection with disseminated tuberculosis, the emergence of resistance should be a concern for the HIV-infected patient with TBM.

HIV-infected individuals are at greater risk for developing rifamycin resistance on therapy, and this risk appears to be closely related to the rifamycin dosing schedule. A twice-weekly rifamycin dosing schedule during the continuation phase has been linked to acquired rifamycin resistance, both with the use of rifampin and rifabutin, and patients with advanced HIV infection (CD4 count < 100) are at greatest risk [43]. Rifapentine, a once-weekly rifamycin, is contraindicated for the treatment of tuberculosis in the HIV-infected patient, due to the risk of relapse with rifamycin monoresistance [44].

Acquired rifamycin resistance in HIV-infected patients may also be related to malabsorption of the anti-tuberculous agents. Among patients with pulmonary tuberculosis in India, HIV-infected individuals had a peak serum rifampin concentration that was only one-half the level measured in HIV-uninfected individuals. Serum isoniazid levels were also significantly decreased in HIV-infected individuals [45]. In a second study by the same investigators, the percent of rifampin dose excreted in urine was positively correlated with CD4+ count, indicating greater malabsorption in patients with more advanced HIV disease [46]. Suboptimal rifamycin levels have been linked to acquired rifamycin resistance, and a role for pharmacokinetic monitoring in the setting of advanced HIV disease has been proposed. For isoniazid, the decreased bioavailability due to malabsorption may be compounded by genetic variations in the rate of isoniazid acetylation, but the role of subtherapeutic isoniazid levels in the emergence of rifamycin resistance is less clear.

Treatment of drug-resistant TBM

Despite the high prevalence of isoniazid resistance worldwide, and the central role that isoniazid may have in effective therapy, there have been few studies evaluating outcomes of isoniazid-resistant TBM. In a prospective study in Vietnam, isoniazid resistance was associated with a longer time to sterility of CSF, compared with isoniazid-susceptible strains [47]. In a second Vietnamese study of nine patients with isoniazid-resistant TBM, there was no significant difference in mortality between the isoniazid-resistant group and the

isoniazid-susceptible group. However, in addition to the small sample size, it is important to note that the group with initial isoniazid resistance contained fewer HIV-positive patients than did the isoniazid-susceptible group, which may have biased the results [48].

TBM due to multidrug-resistant organisms, with resistance to both isoniazid and rifampin, has been described in a number of settings, and the mortality rate is high. In a case series of multidrug-resistant TBM in patients with advanced HIV infection, seven of eight patients had died by 16 weeks following the time of diagnosis. In this series, extrameningeal tuberculosis preceded TBM in all cases, and deaths occurred despite the use of at least two anti-tuberculous agents to which the infecting organisms were susceptible [49]. Among HIV-infected adults in Argentina, multidrug-resistant strains were associated with a significantly increased risk of death during hospitalization [32].

Due to the threat of rapid deterioration, second-line agents should be used early in therapy when drug resistance is suspected [40]. Appropriate second-line agents, with significant concentrations in the CSF, include ethionamide, cycloserine, and fluoroquinolones. Experience with these agents in the treatment of TBM is anecdotal, and clinical trials are needed.

Timing of ART

Although the use of ART during the treatment of tuberculosis may improve clinical outcomes, the timing of initiation of ART relative to anti-tuberculous therapy is complex. In addition to the known drug–drug interactions that are described above, simultaneous initiation of anti-tuberculous therapy and ART leads to overlapping drug toxicities. Initiation of anti-tuberculous therapy in the absence of ART may also be associated with a transient worsening of the signs and symptoms of infection, which is known as the paradoxical reaction. In the cases of TBM, the paradoxical reaction may present as the appearance of multiple tuberculomas after initiation of effective therapy [50]. The paradoxical reaction during treatment of TBM may be exacerbated by immune restoration with ART.

However, the delayed initiation of ART carries its own dangers. In cases of TBM, autopsy studies have found a significant proportion of patients with additional opportunistic infections, including infections of the CNS [25], and this may partly explain the high mortality of co-infected patients who have started anti-tuberculous therapy. Given these competing risks, the optimal timing of initiation of ART in relation to anti-tuberculous therapy has not been established. Until better evidence becomes available, the CDC recommends individualizing this treatment decision, with the possibility of a 4- to 8-week period of anti-tuberculous therapy before initiation of ART [40].

More recently, the SAPIT trial (Starting Antiretroviral Therapy in Tuberculosis) compared the timing of ART relative to anti-tuberculous therapy. Subjects were randomized to one of three arms: initiation of ART simultaneous with anti-tuberculous therapy, initiation of ART following the intensive phase of anti-tuberculous therapy, or initiation of ART at the completion of anti-tuberculous therapy. The first two arms were considered integrated treatment, and the third was considered sequential treatment. Enrollment in the sequential arm of the trial was halted after a hazard ratio of death in the integrated arms was observed to be 0.44 compared with the sequential arm. This mortality difference was observed despite similar tuberculosis outcomes. The trial is ongoing to compare the two arms of integrated treatment. Given these findings, earlier initiation of ART may be the trend in the future [51].

Response to steroids

Corticosteroids are used during the initial treatment of TBM to reduce the detrimental effects of the paradoxical reaction. In a randomized, controlled, clinical trial in Vietnam, the

use of dexamethasone was associated with improved survival at 9 months, but not with decreased morbidity among survivors. Among the subgroup of patients with HIV, there was a reduction in the risk of death at 9 months that was not significant ($P = 0.08$). The HIV-infected patients had a much higher mortality overall, attributed by the authors to presentation with advanced HIV disease (median CD4+ count = 66 per mm^3) and lack of access to ART [26]. More data are needed to determine the exact mechanism by which corticosteroids exert their protective effect in TBM.

Conclusions

The mortality rates of TBM remain high despite the initiation of effective anti-tuberculous therapy. The HIV-infected individual is at greater risk of developing TBM, particularly at a stage of more advanced immunosuppression. Clinical features that may be more common in the HIV-infected individual with TBM include an altered level of consciousness, cerebral infarctions, and a positive CSF culture for *M. tuberculosis*. Furthermore, most observational studies of TBM have found that co-infection with HIV is associated with an increased risk of mortality. Future investigations of pharmacokinetics and clinical outcomes will lead to improved recommendations for dual anti-tuberculous therapy and ART.

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