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SHORT COMMUNICATION

Multidrug-resistant tuberculous meningitis in patients with AIDS

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SUMMARY

We present clinical manifestations, bacteriologic characteristics, and outcomes for eight patients with multidrug-resistant (MDR) tuberculous meningitis and AIDS. All developed meningitis as a terminal complication of previously diagnosed MDR-TB despite anti-tuberculosis therapy. Seven patients presented with fever, five with headache, four with altered mentation, two with focal deficits and one with seizures. CSF examination revealed pleocytosis, hypoglychorrhachia and elevated protein. *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampin was isolated from all patients. Intracerebral mass lesions were detected in three patients, hydrocephalus in three, meningeal enhancement in five, and infarcts in two. Seven patients died 1–16 weeks after the diagnosis of meningitis; the eighth was lost to follow-up. MDR tuberculous meningitis is a difficult-to-treat infection with a high fatality rate.

KEYWORDS: tuberculosis; meningitis; HIV

TUBERCULOUS MENINGITIS accounts for approximately 5% of extra-pulmonary cases or about 0.7% of all clinical tuberculosis (TB) in the United States.[1] This form of TB occurs five times more frequently in human immunodeficiency virus (HIV) positive than in HIV-negative individuals.[2,3] Despite its increased incidence in HIV-infected patients and the emergence of multidrug-resistant (MDR, defined as resistance to at least isoniazid and rifampin) tubercle bacilli worldwide, reports of tuberculous meningitis caused by MDR organisms are rare.[4–8] We present the clinical manifestations, bacteriologic characteristics, and outcomes of eight patients with MDR tuberculous meningitis and AIDS.

MATERIALS AND METHODS

Patients were identified by review of the clinical microbiology laboratory and medical records of Jackson Memorial Medical Center in Miami. Patients with a clinical course consistent with tuberculous meningitis whose cerebrospinal fluid (CSF) culture had grown MDR tubercle bacilli were considered to have MDR tuberculous meningitis. The records were reviewed and pertinent information was abstracted. Mycobacteria were isolated using the BACTEC radiometric method (Becton-Dickinson, Townson, MD). Susceptibility to antimycobacterial drugs was tested by the Florida Department of Health and Rehabilitative Services Mycobacteriology Laboratory in Tampa, using the agar-modified proportional method.[9]

RESULTS

Between January 1988 and December 1999, eight patients were identified with MDR-tuberculous meningitis and HIV infection. Pertinent clinical information is outlined in the Table. The male to female ratio was 3:1. The mean age was 34 years (range 28–45). For all patients an AIDS-defining condition preceded the diagnosis of TB. The absolute CD_4+ T-lymphocyte count at or near the time of TB diagnosis ranged from 9/mm^3 to 118/mm^3 (mean 51/mm^3). Extrameningeal TB preceded the diagnosis of meningitis in all patients. Sputum culture yielded MDR-TB in all patients. Despite the administration of at least two anti-tuberculosis drugs to which the infecting organisms were susceptible, all patients continued to have positive sputum cultures for *Mycobacterium tuberculosis* (97% of examined specimens remained positive).

The time from the diagnosis of TB to progression to meningitis ranged from 2 to 14 months (median 3.5, mean 6.1). Seven patients presented with fever ($\geqslant$38°C), five with headache, four with vomiting, and one with seizures. Altered mentation was present in four patients: two were confused, one lethargic, and one comatose. Meningismus was present in six patients and focal deficits in two. Four patients had stage I disease, three had stage II, and one had stage III, according to British Medical Research Council criteria.[11] Sputum examination demonstrated acid-fast bacilli and sputum cultures yielded *M. tuberculosis* in all

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Table Clinical manifestations of eight patients with multidrug-resistant tuberculous meningitis and AIDS

Patient no.	1	2	3	4	5	6	7	8
Age (years)/sex	28/F	29/M	33/M	41/M	24/M	37/M	45/M	40/F
CDC category[10]	C_3	C_3	C*	C_3	C_3	C_3	C_3	C_3
Site of TB at time of diagnosis	Pulmonary, pleural	Pulmonary, pleural	Miliary	Pulmonary	Pulmonary	Pulmonary, pleural	Pulmonary, lymphatic	Pulmonary, lymphatic
Sputum examination for *M. tuberculosis*								
Smear (positive/total)	5/6	4/4	4/4	1/1	1/3	3/3	6/7	4/5
Culture (positive/total)	6/6	4/4	4/4	1/1	3/3	3/3	7/7	4/5
Time from diagnosis of TB to progression to meningitis (mo)	14	5	2	2	11	2	2	11
Clinical manifestations								
Fever	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Mental status	Confused	Lethargic	Conscious	Conscious	Conscious	Confused	Conscious	Comatose
Meningismus	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Focal deficits	No	Yes	No	No	No	No	No	Yes
Seizures	Yes	No	No	No	No	No	No	No
MRC stage	II	II	I	I	I	II	I	III
Analysis of CSF								
Protein (mg/dl)	801	317	274	153	257	379	73	196
Glucose (mg/dl)	38	26	15	38	27	35	45	13
WBC/lymph (mm^3/%)	133/98	240/60	1389/19	180/19	620/59	9/100	41/93	1292/62
Culture	*M. tuberculosis*	*M. tuberculosis*	*M. tuberculosis*	*M. tuberculosis*	*M. tuberculosis*	*M. tuberculosis*	*M. tuberculosis*	*M. tuberculosis*
Drug resistance	H, R	H, R, ETH, E	H, R, ETH	H, R, ETH	H, R, ETH	H, R, ETH	H, R, ETH, E	H, R, ETH
Brain CT or MR	ME	ME, infarct, hydrocephalus	Atrophy	Mass	ME, mass	ME, mass, hydrocephalus	Normal	ME, infarct, hydrocephalus
Treatment	H, Z, CS, S	H, R, CS, Z, AM	H, R, Z, E	H, R, Z, E	H, E, AM, CS, CIP, Z, PAS	R, Z, S	H, R, E, Z, S	E, CIP, Z, CS, S
Time from diagnosis of TB meningitis to death (wks)	4	4	1	2	Lost to follow-up	4	16	11

* CD_4+ T-cell count not available.
M = male; F = female; CDC = Centers for Disease Control and Prevention; MRC= British Medical Research Council; CSF = cerebrospinal fluid; WBC = white blood cell; H = isoniazid; R = rifampin; ET = ethionamide; E = ethambutol; TB = tuberculosis; CT = computed tomography; MR = magnetic resonance; ME= meningeal enhancement; Z = pyrazinamide; CS = cycloserine; S = streptomycin; AM = amikacin; CIP = ciprofloxacin; PAS = para-aminosalcylic acid.

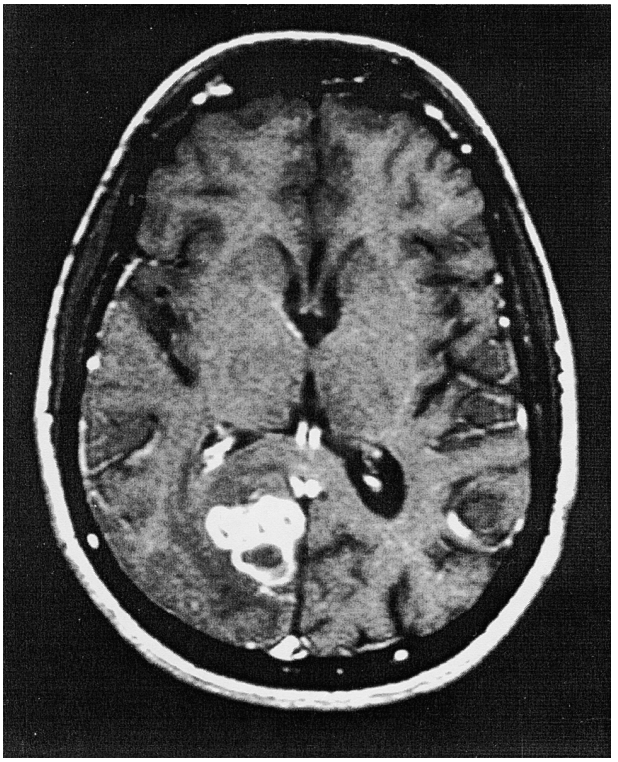

Figure Axial post-contrast T1W sequence of patient no 5 with a biopsy-proven tuberculous abscess. Note the multilocular enhancing mass lesion with surrounding oedema in the right occipital lobe; meningeal enhancement is also seen.

seven patients from whom sputum had been obtained at or near the time of diagnosis of tuberculous meningitis. Chest radiographs were abnormal in all patients; six had pulmonary infiltrates with alveolar and two with interstitial patterns. Paratracheal and/or hilar lymphadenopathy was noted in four patients, pleural effusion in two, and cavitation in one. CSF fluid cultures of all patients grew *M. tuberculosis* with the same susceptibility pattern. Cranial computed tomography (CT) or magnetic resonance (MR) scans were abnormal in seven of the eight patients: five demonstrated meningeal enhancement, three mass lesions, three hydrocephalus, two infarcts and one atrophy. The intracerebral mass lesions in Cases 5 (Figure) and 6 were tuberculous abscesses, and in Case 4 it was tuberculoma, as demonstrated by aspiration of the lesions in the first two cases and at autopsy in the third case. Seven patients died, and the eighth was lost to follow-up after discharge from hospital. The time from diagnosis of meningitis to death ranged from 1 week to 4 months (median 1 month, mean 1.5 months).

DISCUSSION

The eight cases of MDR tuberculous meningitis occurred during a nosocomial outbreak of MDR-TB in our institution.[12] Of special note is the fact that meningitis occurred in those patients with MDR-TB who had survived longer: the median survival time for patients with MDR-tuberculous meningitis, from diagnosis of TB to death, was 6 months compared to 1.5 months for all patients with MDR-TB and AIDS diagnosed in our institution during that period. In the first group the longer survival time apparently increased the chances for tubercle bacilli to disseminate and establish foci of infection at critical locations in the central nervous system (CNS) that subsequently ruptured into the subarachnoid space, resulting in meningitis.

Previous studies have shown that HIV infection has little impact on the clinical manifestations of tuberculous meningitis.[2,3] Although our patients had certain clinical features similar to those with tuberculous meningitis caused by susceptible organisms, their clinical course was quite distinctive. All cases in this series developed meningitis as a terminal complication of previously diagnosed MDR-TB that did not respond to anti-tuberculosis therapy. Moreover, all patients had radiologic and bacteriologic evidence of active pulmonary infection throughout the period, from diagnosis of TB to progression to meningitis, whereas in a recent study 65% of 37 HIV-infected patients with tuberculous meningitis had concurrent extrameningeal TB.[2] Progression of TB and dissemination of bacilli to the CNS or other organs, despite administration of anti-tuberculosis therapy, may provide the first indication of infection with MDR organisms.

The neuroradiographic findings in the present series covered the whole spectrum of manifestations for CNS TB: meningeal enhancement, hydrocephalus, infarcts, and intracranial mass lesions. Intracranial mass lesions are rare manifestations of TB in the industrialized world, and appear in the form of tuberculomas or tuberculous abscesses. Tuberculous abscess is seen in 4%–8% of patients with CNS TB without HIV infection. Recent reports, however, suggest that such lesions occur with increasing frequency among HIV-positive individuals.[2,3,13,14] In agreement with these observations, tuberculous abscess was present in 25% of patients in the present series and appeared as single multilocular enhancing lesions. These radiographic findings may represent distinct characteristics of tuberculous brain abscess and serve as diagnostic clues to this clinical entity.[14]

The fatality among our patients was significantly higher than reported previously in HIV-infected patients with tuberculous meningitis.[2,3] Although HIV infection does not appear to influence the outcome of the disease, patients with lower CD_4+ T-cell counts had significantly lower survival rates.[2,3] Fatality rates for tuberculous meningitis currently range from 6% to 27%, and depend mainly on the clinical stage of the disease at diagnosis. Other factors that may affect survival include the duration of the illness, the presence

of miliary disease, and very young or old age.[15–17] Although in the present series it was not possible to identify factors related to mortality, the dismal outcome of our patients was attributed to two factors: 1) the profound immune dysfunction of the host, as indicated by severe CD_4+ T-cell depletion, and 2) infection with organisms resistant to both isoniazid and rifampin.

Isoniazid is the keystone of treatment of tuberculous meningitis;[18] it is bactericidal, and because of its high lipid solubility, small molecular weight, and lack of ionization, it penetrates readily into the CSF. Rifampin penetrates into the CSF rather slowly, and makes a modest contribution to the treatment of tuberculous meningitis. The contribution to the treatment of tuberculous meningitis of the third agent that has revolutionized the treatment of pulmonary TB, pyrazinamide, is doubtful, although it penetrates well into the CSF. Other agents such as streptomycin and ethambutol cross the blood-brain barrier poorly, resulting in suboptimal concentrations in CSF. Therefore, CNS disease caused by tubercle bacilli resistant to both isoniazid and rifampin will be very difficult to manage. Seven of the eight patients presented here (one was lost to follow-up) and four of six previously reported with MDR tuberculous meningitis died.[4–8] The two patients that survived this usually fatal form of the disease were HIV-negative and were treated successfully with systemic and intrathecal administration of anti-tuberculosis drugs.[7,8] This novel treatment regimen, along with highly active antiretroviral therapy, might change the poor outcome of MDR tuberculous meningitis in the setting of HIV infection.

This series demonstrates the clinical features and high fatality rate of MDR tuberculous meningitis in the setting of advanced HIV infection. As HIV infection increases the community burden of TB and the spread of MDR tubercle bacilli is continuing in certain geographic regions, more cases of MDR tuberculous meningitis are expected. New treatment modalities are therefore urgently needed, and optimal therapy remains to be defined for this difficult-to-treat form of tuberculosis.

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RÉSUMÉ

Nous décrivons les manifestations cliniques, les caractéristiques bactériologiques et les résultats chez huit patients atteints de méningite tuberculeuse à germes multirésistants (MDR) et de SIDA. Tous les patients ont développé une méningite comme complication terminale d'une tuberculose à germes multirésistants diagnostiquée antérieurement et ce malgré l'administration d'un traitement antituberculeux. Sept patients ont consulté pour fièvre, cinq pour céphalées, quatre pour troubles mentaux, deux pour un déficit focal et un pour convulsions. L'examen du liquide céphalo-rachidien a mis en évidence une augmentation du nombre d'éléments cellulaires, une hypoglycorachie et un taux élevé de protéines. *Mycobacterium tuberculosis* résistant au moins à l'iso-

niazide et à la rifampicine a été isolé chez tous les patients. On a détecté des masses intracérébrales chez trois patients, de l'hydrocéphalie chez trois, des épaississements méningés chez cinq et des infarctus chez deux. Sept patients sont décédés dans les 1 à 16 semaines après le diagnostic de méningite et le huitième a été perdu de vue. La méningite tuberculeuse à germes multirésistants est difficile à traiter et s'accompagne d'un taux élevé de décès.

RESUMEN

Se presentan las manifestaciones clínicas, las características bacteriológicas y los resultados del tratamiento de ocho pacientes con meningitis tuberculosa multirresistente (MR) y SIDA. Todos los pacientes desarrollaron una meningitis como complicación terminal de una tuberculosis MR previamente diagnosticada, a pesar de la administración de un tratamiento antituberculoso. Siete pacientes consultaron por fiebre, cinco por cefalea, cuatro por alteraciones mentales, dos por déficits focales y uno por convulsiones. El examen de líquido céfalorraquídeo reveló una pleocitosis, una hipoglucorraquia y una tasa elevada de proteínas. En todos los pacientes se aisló *Mycobacterium tuberculosis* resistente al menos a la isoniacida y a la rifampicina. En tres pacientes se detectaron masas intracerebrales, en tres hidrocefalia, en cinco engrosamiento meníngeo e infarto en dos. Siete pacientes fallecieron entre 1 y 16 semanas después del diagnóstico de la meningitis y el último fue perdido de vista. La meningitis tuberculosa MR es difícil de tratar y tiene una alta tasa de letalidad.