Multidrug-Resistant Tuberculous Meningitis in KwaZulu-Natal, South Africa

V. B. Patel,[1] N. Padayatchi,[2] A. I. Bhigjee,[1] J. Allen,[3] B. Bhagwan,[1] A. A. Moodley,[1] and T. Mthiyane[3]

[1]Department of Neurology and [2]Centre for the AIDS Program for Research in South Africa (CAPRISA), Nelson R. Mandela School of Medicine, University of Natal, and [3]Unit for Clinical and Biomedical TB Research, Medical Research Council, Durban, South Africa

Multidrug-resistant (MDR) pulmonary tuberculosis (TB) is well described in the literature. Reports of MDR TB meningitis (MDR-TBM), however, are limited to case reports and a single case series. During the period of 1999–2002, 350 patients with TBM were identified by cerebrospinal fluid culture for TB. Thirty patients (8.6%) had TB that was resistant to at least isoniazid and rifampicin. All 30 patients were included in this study. We reviewed hospital charts of the patients with MDR-TBM and describe our experience. Seventeen patients with MDR-TBM died, and, of those who were known to be alive, many experienced significant morbidity. Eighteen patients were HIV positive. Twenty-two patients had been treated for TB in the past, 3 patients had received no previous treatment for TB, and the history of TB treatment was unknown for 5 patients. The study highlights the prevalence of MDR-TBM and identifies new challenges in the management of affected patients.

Tuberculosis (TB) has reemerged as a global epidemic. Recent data from the World Health Organization (WHO) suggest that the global incidence is increasing by 0.4% per annum [1]. In South Africa, the number of notifications increased from 55,310 cases per annum in 1980 to 148,257 cases per annum in 2001. The prevalence increased from 190 cases per 100,000 people in 1980 to 339 cases per 100,000 people in 2001 [2]. This has been complicated by the emergence of multidrug-resistant pulmonary TB. In South Africa, the mean prevalence of multidrug-resistant pulmonary TB is 1.6% (range, 0.3%–3.3%) among treatment-naive patients and 6.7% (range, 1.7%–18.8%) among patients who have previously been treated for TB [3]. In the province of KwaZulu-Natal, the prevalence of multidrug-resistant pulmonary TB among treatment-naive patients is 1%–2%, and it is 7%–8% among those who have previously been treated for TB [3].

The HIV epidemic contributes to the increasing TB disease burden and to consequent morbidity and mortality. CNS TB accounts for 5% of all cases of extrapulmonary TB, and meningitis is the most frequent complication [4]. Against this background, we anticipate an increase in multidrug-resistant TB meningitis. To date, single case reports and a single case series about multidrug-resistant TB meningitis have been reported [5]. We report our experience with a cohort of 30 patients with multidrug-resistant TB meningitis in KwaZulu-Natal and discuss the case histories of 2 health workers in detail.

METHODS

In the public hospitals in KwaZulu-Natal, CSF cultures are performed at a central laboratory. Samples collected from 1999 through 2002 that yielded multidrug-resistant TB were included in the study. The biochemical and cellular changes in the CSF and the resistance patterns noted for these cultures were recorded. After consent was obtained from the relevant hospital managers, demographic and clinical data were acquired from the

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Reprints or correspondence: Dr. Padayatchi Nesri, Nelson R. Mandela School of Medicine, University of Natal, Private Bag X7, Congella Durban 4013, South Africa (padayatchin@nu.ac.za).

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hospital charts for the patients from whom these samples were obtained.

Multidrug-resistant TB was defined as *Mycobacterium tuberculosis* that was resistant to at least isoniazid and rifampicin. All of the patients we describe had TB that was resistant to at least these 2 drugs.

The British Medical Research Council (BMRC) system for grading meningitis was used to describe the neurological status of patients, as follows: grade 1, patient was fully conscious and rational, and there were no neurological signs; grade 2, patients was confused but not comatose or had neurological signs, such as hemiparesis or single cranial nerve palsy; and grade 3, patient was comatose or stuporose or had multiple cranial nerve palsies or complete hemiplegia or paraplegia.

RESULTS

Clinical data are summarized in table 1. During the study period, a total of 6762 CSF samples obtained for culture for *Mycobacterium tuberculosis.* There were 350 cultures positive for *M. tuberculosis* (5.2%), 40 (11.4%) of which yielded multidrug-resistant *M. tuberculosis.* After excluding additional culture specimens obtained single patients, the sample size was reduced to 30 patients (8.6%).

Table 1. Clinical data for patients in a study of multidrug-resistant tuberculous (TB) meningitis in KwaZulu-Natal, South Africa.

Patient	Age, years	Sex	HIV infection status	Past history of TB treatment	BMRC meningitis grade	Received prednisone	Received adequate TB treatment	Outcome
1	27	F	+	Yes	2	No	No	Died
2	18	F	+	Yes	1	No	No	Improved
3	32	F	+	Yes	1	Yes	No	Improved
4	28	F	+	Yes	1	Yes	No	Died
5	11	F	+	Yes	1	No	No	Died
6	18	F	+	Yes	2	Yes	Yes	Died
7	18	F	−	Yes	2	Yes	Yes	Improved
8	37	M	+	Yes	2	Yes	No	Died
9	31	F	+	Yes	2	Yes	No	Died
10	27	F	NA	Yes	2	Yes	No	Improved
11	45	F	NA	Yes	1	No	No	Improved
12	30	M	+	Yes	1	Yes	No	Died
13	36	M	NA	Yes	3	Yes	No	Died
14	20	F	+	Yes	3	Yes	Yes	Improved
15	24	F	+	Yes	1	Yes	Yes	Improved[a]
16	29	F	NA	NA	NA	NA	NA	NA
17	26	F	−	No	3	Yes	Yes	Improved
18	29	M	NA	Yes	3	No	No	Died
19	0.4	F	NA	NA	NA	Yes	Yes	Died
20	8	M	+	No	2	Yes	Yes	Improved[a]
21	21	F	+	Yes	3	No	No	Died
22	20	F	+	Yes	1	Yes	No	Died
23	32	M	+	Yes	1	No	No	Died
24	24	F	NA	Yes	3	No	No	Died
25	34	F	+	Yes	1	No	No	Died
26	28	F	+	No	2	No	No	Died
27	31	M	+	NA	1	Yes	No	Died
28	29	M	NA	Yes	1	No	No	Improved
29	NA	NA	NA	NA	NA	NA	NA	NA
30	NA	NA	NA	NA	NA	NA	NA	NA

NOTE. BMRC, British Medical Research Council; NA, not available; +, positive, −, negative.

[a] Receiving antiretroviral therapy.

The mean age was 25.7 years (median age, 28 years; range, 0.4–45 years). There were 21 female patients (70%) and 9 male patients (30%). Two patients had cryptococcal meningitis in addition to multidrug-resistant TB meningitis. Twenty-two patients (73%) had a history of prior exposure to anti-TB therapy, 3 patients (10%) had not previously received treatment for TB, and this information was not known for 5 patients (17%).

Only 2 patients were known to be HIV negative (table 1), and these were health care workers who probably acquired multidrug-resistant TB ab initio. Their conditions improved while receiving treatment, but they were left with significant functional impairment. These patients are described in Case Reports.

The BMRC clinical assessment rating for meningitis was grade 1 for 8 patients (26.7%), grade 2 for 11 patients (36.7%), and grade 3 for 8 patients (26.7%). The clinical grade was unknown in 3 patients (10%). Eighteen patients were HIV positive (13 of these patients died and 5 were alive), and the HIV infection status was unknown for 10 patients (4 of these patients died, 3 were alive, and 3 had unknown outcomes).

Fourteen patients also had pulmonary TB; 2 of these patients had a miliary pattern (1 with dissemination), and 4 patients had proven multidrug-resistant pulmonary TB. One patient had an exudative pleural effusion. In 9 patients, there was no evidence of TB in any other organ, and, for 6 patients, it was not known whether there was other organ involvement.

Table 2. CSF changes and drug susceptibilities in a study of multidrug-resistant tuberculous meningitis in KwaZulu-Natal, South Africa.

Patient	PML count, cells/μL	Lymphocyte count, cells/mL	Protein level, g/L	Glucose[a] level, mmol/L	Chloride level, mmol/L	Cryptococcal antigen	Susceptibility profile								
							Inh	Rif	Emb	Sm	Eth	Kan	Ofl	Th	Cy
1	70	570	7.9	1.4	114	−	R	R	R	S	S	S	S	S	S
2	0	88	0.7	1.1	127	+	R	R	S	S	S	S	S	S	S
3	10	58	0.7	2.2	115	−	R	R	S	S	S	S	S	S	S
4	14	36	2.7	1.9	105	−	R	R	S	R	R	S	NA	S	S
5	NA	NA	NA	NA	NA	NA	R	R	S	R	R	S	S	S	S
6	68	210	ND	ND	101	−	R	R	R	R	R	S	S	S	R
7	92	106	0.8	1.6	100	−	R	R	R	R	S	S	S	S	S
8	0	4	0.6	0.0	126	−	R	R	R	R	R	R	S	S	S
9	0	0	0.7	2.1 (6.3)	118	−	R	R	R	R	R	S	S	R	R
10	80	120	2.6	1.3	119	−	R	R	R	S	R	S	S	S	S
11	2	118	2.5	1.2 (5.9)	115	−	R	R	R	R	R	S	S	S	S
12	28	42	5.4	0.7 (4.3)	115	−	R	R	S	R	S	S	S	S	S
13	190	200	2.4	2.6 (10.1	113	−	R	R	S	R	S	S	S	S	S
14	114	305	1.7	1.0	114	−	R	R	R	R	R	S	S	S	S
15	32	40	1.4	1.8	119	−	R	R	S	R	R	S	S	S	S
16	NA	NA	NA	NA	NA	NA	R	R	S	R	S	S	S	S	S
17	4	2	1.6	1.9 (4.9)	117	−	R[b]	R[b]	R[b]	S[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]
18	10	76	0.3	1.1	95	−	R	R	S	R	S	S	S	S	S
19	22	126	2.7	0.7	103	−	R	R	S	S	S	S	S	S	S
20	10	10	1.3	1.7	124	−	R	R	S	S	S	S	S	S	S
21	56	16	0.7	2.3	100	−	R	R	R	R	S	S	NA	S	S
22	60	610	7.8	1.2 (4.2)	114	−	R	R	S	R	S	S	NA	S	S
23	30	385	18.0	1.8	104	−	R	R	S	R	R	S	NA	S	R
24	NA	NA	NA	NA	NA	NA	R	R	S	S	R	S	S	S	S
25	860	350	6.5	0.9	105	−	R	R	R	R	R	S	S	S	S
26	0	0	0.5	2.4	124	+	R	R	S	S	S	S	S	S	S
27	630	30	1.6	0.5	116	−	R	R	S	R	S	S	S	S	S
28	230	120	17.3	2.1	109	−	R	R	S	R	R	S	S	S	S
29	NA	NA	NA	NA	NA	NA	R	R	R	R	R	R	S	R	S
30	NA	NA	NA	NA	NA	NA	R	R	S	S	R	S	NA	S	S

NOTE. Cy, cycloserine; Emb, ethambutol; Eth, ethionamide; Inh, isoniazid; Kan, kanamycin; NA, not available; ND, not done; Ofl, ofloxacin; PML, polymorphonuclear leukocyte; R, resistant; Rif, rifampin; S, susceptible; Sm, streptomycin; Th, thiacetazone; +, positive; −, negative.

[a] CSF glucose.

[b] Isolate was recovered from a sphenoidal biopsy specimen; CSF culture results were negative.

The CSF findings and culture susceptibility data are summarized in table 2. In patients 9 and 26, there were no cells detected in the CSF specimen (one patient had pleural effusion, and the other had parenchymal lung disease). Both patients died within a few days after hospital admission. For 2 patients (patients 8 and 17), <6 cells were noted in the CSF specimen; both patients also had pulmonary TB. One patient died, and the other has responded to appropriate drug therapy (see patient 17 in Case Reports).

Resistance was noted for the agents ethambutol (12 patients), streptomycin (20 patients), ethionamide (15 patients), kanamycin (2 patients), thiacetazone (2 patients), and cycloserine (2 patients). Tests for pyrazinamide susceptibility are not available in KwaZulu-Natal; therefore, the susceptibility of *M. tuberculosis* to this drug is not known. The occurrence of mycobacterial isolates that were resistant to many more drugs than just isoniazid and rifampicin (table 3) is of additional concern. Nine patients were infected with *M. tuberculosis* that was resistant to rifampicin, isoniazid, ethambutol, and streptomycin. Seven patients were infected with strains that were resistant to rifampicin, isoniazid, ethambutol, streptomycin, and ethionamide. Five patients were infected with strains that were resistant to only rifampicin and isoniazid.

Only 7 patients were treated with drugs to which the organism was susceptible. Sixteen patients were treated with prednisone, and, for 3 patients, treatment information was not known. Of the 7 patients who received both appropriate TB treatment and prednisone, 2 died. Of the remaining 5 patients whose conditions improved, 2 also received antiretroviral drugs.

Table 3. Drug resistance among 30 multidrug-resistant CSF culture isolates from KwaZulu-Natal, South Africa.

No. of drugs to which isolate was resistant	No. of patients with resistant isolate
2	5
3	10
4	7
5	4
6	2
7	2

CASE REPORTS

Patient 7. A 19-year-old student health care worker presented with cough, chest pain, general malaise, and fever. On the basis of findings from a chest radiograph and sputum smear results (culture results were negative), pulmonary TB was diagnosed, and the student was treated for 6 months with first-line anti-TB therapy (i.e., rifampicin, isoniazid, pyrazinamide, and ethambutol). Nine months later, she presented again with TB lymphadenopathy, which was confirmed histologically. On this occasion, a second chest radiograph revealed that the previously treated pneumonia had not resolved. The patient restarted standard first-line anti-TB therapy and developed drug-induced hepatitis, for which she was referred to the regional TB hospital for inpatient management.

Clinical evaluation confirmed asthenia, jaundice, and lymphadenopathy, and the findings of a neurological examination were normal. The patient's chest radiograph showed lobar pneumonia. While receiving treatment, she developed a seizure, and she was investigated for meningitis. Her clinical grade, CSF changes, and outcome are summarized in tables 1 and 2. The findings of the initial computerized axial tomography scan of the brain were unremarkable. Despite receiving treatment, she became obtunded and developed hyponatremia and hydrocephalus. The hydrocephalus was corrected with a ventriculoperitoneal shunt, and the patients mental state improved. Isoniazid- and rifampicin-resistant TB bacilli were isolated from CSF specimens. A second-line treatment regimen that included ethionamide, cycloserine, ciprofloxacin, and amikacin was added to therapy. Her clinical course was complicated by a pontine infarct. The patient is currently quadrispastic, and although she is alert, she remains "locked in" (i.e., the patient is fully awake but unable to move or communicate). The most recent CSF and sputum culture results were negative.

Patient 17. A 26-year-old health care worker presented to her physician with a 3-week history of fever, weakness, and malaise. She completed a course of antibiotics, but her condition did not improve. A chest radiograph showed left upper lobe infiltration and left hilar lymphadenopathy. A presumptive diagnosis of pulmonary TB was made, and treatment with first-line anti-TB drugs and pyridoxine was commenced. The patient then complained of headache and vomiting. Four weeks after onset of symptoms, she had a generalized seizure. She became jaundiced and also had neck stiffness. The findings of an initial CT scan of the brain with contrast were normal. The CSF findings were consistent with TB meningitis (tables 1 and 2).

MRI of the brain was performed 2 months later and showed basal enhancement and sphenoidal sinusitis. The neck stiffness worsened, and the patient developed bilateral abducens nerve palsies and a right facial nerve palsy. A brain CT performed at this time revealed hydrocephalus. A ventriculoperitoneal shunt was inserted.

During the interval between the initial CT and the MRI, multidrug-resistant *M. tuberculosis* was cultured from a sputum sample and also from fluid from the sphenoid sinus. The treatment regimen was changed to pyrazinamide, ofloxacin, cycloserine, ethionamide, amikacin, pyridoxine, and prednisone.

When assessed 6 months after the onset of illness, the patient's condition had stabilized, but the patient had grade 4/5 weakness of both arms and legs, right facial weakness, and resolving sixth nerve palsies. An additional MRI, which included the cervical spine, still showed extensive meningeal enhancement, and ischemic lesions in the pons and left basal nuclei were noted.

DISCUSSION

Treatment for TB meningitis is usually initiated when there is clinical suspicion, because any delay in treatment results in significant morbidity, and failure to treat is associated with a high case-fatality rate. The low sensitivity of CSF smears and culture and the prolonged time required for culturing and susceptibility testing make TB meningitis a difficult diagnosis to confirm. Thus, the findings underestimate the true incidence of multidrug-resistant TB meningitis. The emergence of multidrug-resistant TB meningitis complicates the management of TB meningitis, because the first-line anti-TB regimen is inadequate, and there is an additional delay before the susceptibility pattern is known. The total duration of the delay could be up to 10 weeks, leading to even greater morbidity and mortality. There is an urgent need for more sensitive and rapid diagnostic techniques that can be implemented in resource-poor settings, but these are unlikely to be forthcoming in the next few years. Our study supports the findings in the literature that patients with multidrug-resistant TB are likely to have a history of previous treatment for TB. It is disconcerting that 2 patients in this cohort had TB that was resistant to 7 drugs. The implication of this high level of resistance is that there were only 3 drugs available to treat these patients. If translated into epidemic proportions, such cases would be extremely difficult to manage, and there would be devastating consequences. These "pan-resistant" organisms have also been isolated in Peru [6].

The published data on multidrug-resistant TB meningitis is confined to single case reports and a short case series [7–10]. These reports also highlight the morbidity and mortality associated with multidrug-resistant TB meningitis. Our cohort comprises young individuals, most (70%) of whom were female. Seventeen patients died, and those who survived were left with significant functional impairment. There was no definitive association between clinical grade, administration of prednisone, and outcome, although we acknowledge that the sample size was small. However, most of the culture and susceptibility test results were received after the patients had died or had been discharged from the hospital; as a consequence, only a few patients received appropriate treatment, which may account for the poor outcomes. Contributing factors associated with mortality were comorbid disease related to other organ involvement (such as liver dysfunction, bone marrow phthisis, and respiratory dysfunction) and receipt of inappropriate treatment for TB (CSF susceptibility results became available posthumously). Of the patients for whom a history of previous treatment for TB was known, only 2 patients (a health care worker and a child) were not treated for TB previously.

Established factors that contribute to TB drug resistance are $\geqslant$1 of the following variables: an erratic drug supply, prescription of inadequate chemotherapy, poor patient management, and nonadherence to therapy and treatment interruptions [11]. In South Africa, despite the implementation of the WHO's directly observed therapy short-course (DOTS) strategy, cure rates for drug-susceptible pulmonary TB improved from 34% to only 54% [2]. This translates into higher rates of multidrug-resistant pulmonary and consequent extrapulmonary TB. The HIV epidemic further fuels the TB epidemic [12–16], and unless interventions are introduced to improve cure rates for drug-susceptible TB, the prevalence of multidrug-resistant TB will be aggravated.

Poorly managed TB-control programs, together with the HIV epidemic, will result in more cases of multidrug-resistant TB and, consequently, a larger number of cases of multidrug-resistant TB meningitis, with considerable morbidity and mortality. This poses a greater management challenge for the physician. From a public health point of view, a more aggressive case finding and treatment campaign is needed to control the pool of multidrug-resistant TB, which has caused institutional outbreaks with high rates of transmission in the United States, Europe, and Latin America.

In countries where multidrug-resistant TB is a growing problem and HIV infection has already reached epidemic proportions, adopting the DOTS strategy alone is insufficient to control the spread of TB [17]. In settings such as these, where health care workers are exposed to patients with undiagnosed and/or inappropriately treated multidrug-resistant TB, rigorous infection-control measures must be implemented to reduce the risk of nosocomial transmission. In the local TB hospital, the HIV seroprevalence among patients with multidrug-resistant pulmonary TB who consented to HIV testing is 22% (N. Padayatchi, personal communication). In this study, 18 patients (60%) were HIV seropositive, 2 (7%) were HIV seronegative, and the HIV infection status was unknown for 10 patients (33%). Among the patients with a known outcome, the mortality rate was 56%. Seventy-six percent of the patients who died had HIV infection. The subsequent outcome for patients who were documented as having "improved" is also unknown, and they may well have had a similar fate.

Management of multidrug-resistant TB in South Africa is 100 times more expensive than is management of drug-susceptible TB, and second-line anti-TB drugs are not as effective as first-line drugs: with the exception of ethionamide, the CSF penetration is poor. There is also a paucity of phar-

macokinetic data for drugs such as cycloserine and thiacetazone [18–20]. Similarly, there are insufficient data regarding the effectiveness of the second-line drugs against intracellular organisms. With the exception of the fluoroquinolones, the other drugs are bacteriostatic. The CSF concentration of ciprofloxacin has only reached 16%–20% of the serum levels in phase 1 trials [21], and these levels may not be adequate for efficacy against slow-growing organisms like *M. tuberculosis*. Because there have not been any controlled studies, the optimal combination of drugs and the duration of therapy are empirical. Although studies have shown that the response to standard anti-TB therapy is similar in patients with drug-susceptible TB meningitis, regardless of HIV infection status [5, 22–25], the response in patients with multidrug-resistant TB meningitis is unknown. Anecdotal reports indicate that the response is poor.

Clinical trials are required to systematically study the second-line drugs so that national protocols can be developed. In the interim, the guidelines of the British Thoracic Society [26] may be adopted. A history of prior exposure to anti-TB drugs in a patient with signs and symptoms of meningitis should alert the clinician to the possibility of multidrug-resistant TB meningitis, and an aggressive approach to investigating such patients is advocated.

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